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THE PEDIATRIC AND AYA ONCOLOGY ISSUE

Survivorship Care

Tips for Caring for Patients Who Have Been Treated for Childhood Cancer

LISA DILLER, MD

Although recent research shows improvement in long-term survival rates for childhood cancer patients,[1] it also highlights the challenges that remain[2] for many of the almost 400,000 survivors in the United States. Other research[3] illustrates that most primary care physicians do not feel comfortable treating survivors of pediatric cancer. As the number of survivors continues to increase, many internists, pediatricians, and obstetrician/gynecologists (OB-GYNs) with busy practices will have at least a few patients who had pediatric cancer under their care. Here I provide suggestions on how to approach a childhood cancer survivor in your practice, several useful resources, and information on what referrals and tests may be indicated.

PATIENTS SHOULD HAVE OR OBTAIN A CANCER TREATMENT SUMMARY AND SURVIVORSHIP PLAN

Children transitioning back to their primary care pediatrician will most likely return with a treatment summary from their cancer centers, along with guidance on surveillance for disease recurrence in the immediate post-therapy period. Longer term follow-up care plans, with screening for late sequelae, should be developed with the help of the treating oncologist.

Adult survivors of childhood cancer should provide their internist or OB-GYN with treatment summaries and survivorship plans; however, many survivors do not have a summary. If a patient does not have a treatment summary, encourage him or her to ob-

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Fertility Preservation

LIVESTRONG Fertility Training: *Addressing the Needs of AYA Cancer Survivors*

BREE HEMINGWAY, MPH; ADITI NARAYAN, MSW; SARAH AVERY, PHD

Survival rates for individuals diagnosed with cancer have increased over the last 30 years, with two-thirds of the more than 14.5 million cancer survivors in the United States living beyond 5 years post treatment.[1,2] These increased survival rates have drawn the attention of the oncology community beyond treatment regimens, causing it to consider the long-term needs of cancer survivors, including their physical and emotional quality of life (QOL) after cancer.

The Institute of Medicine's 2005 report, From Cancer Patient to Cancer Survivor: Lost in Transition, brought to light the challenges faced by the medical community when addressing the needs of cancer survivors post treatment and the importance of comprehensive, coordinated care that improves QOL during cancer survivorship.[3] For adolescent and young adult (AYA) cancer survivors who want the option of having biological children, infertility caused by their cancer and its treatment can be one of the most challenging post-treatment issues they face.[4]

Annually, more than 130,000 patients receive a cancer diagnosis during their reproductive years (younger than 45 years).[1,2] Fortunately, the 5-year survival rate for these patients is 79%. However, the toxic effect of cancer treatment can have negative effects on fertility and QOL.[5,6] Research shows that the ability to have biological children is important to many AYAs who have cancer.[7] However, these survivors may not have all of the information and resources necessary to make an in-

(continued on page SP500)

Mental Health

Bridging the Care Gap Between Pediatric and Young Adult Cancer

LAUREL BAROSH, MPH; TERRY CHURCH, MA, MS; DEBORAH MORGAN, MSN, RN, OCN; MEGAN BIANCHETTI, MSW; JAMES HU, MD, FACP; DEBU TRIPATHY, MD; STUART E. SIEGEL, MD

BACKGROUND

About 70,000 adolescent and young adult (AYA) cancer patients, aged 15 to 39 years, are newly diagnosed annually in the United States; this includes an estimated 4000 or more in the Los Angeles Basin alone. Despite tremendous advancements achieved in pediatric and older adult cancers, the relative improvement in the survival rates and outcomes for AYA patients has not kept pace. For instance, from 1975 to 1997, the average annual improvement in 5-year survival rates for invasive cancers was 1.5% for all ages; however, improvement averaged only 0.5% for cancers in the entire AYA population, and survival actually decreased by -0.18% for individuals aged 30 to 34 years.[1]

During the past 10 years, the so-called "AYA gap" has become the subject of national focus and attention. It has been well documented that AYA patients with cancer often fall through gaps in their clinical and supportive care.[2-5] An understanding of the unique characteristics and outcomes of this group is a continued need. The shared norms, attitudes, and beliefs that determine their behavior as well as the stressors encountered on a daily basis (such as identity formation, body image concerns, sexual relationships, independence from parents, autonomous decision making, as well as educational, career, and personal growth goals) impact the ability of an AYA to cope with cancer.[3]

(continued on page SP501)

A SURVIVOR'S STORY

A young cancer survivor, Woodrow Roseland, shares the impact of surviving cancer and its treatment on his personality (**SP482**).

Also in this issue...

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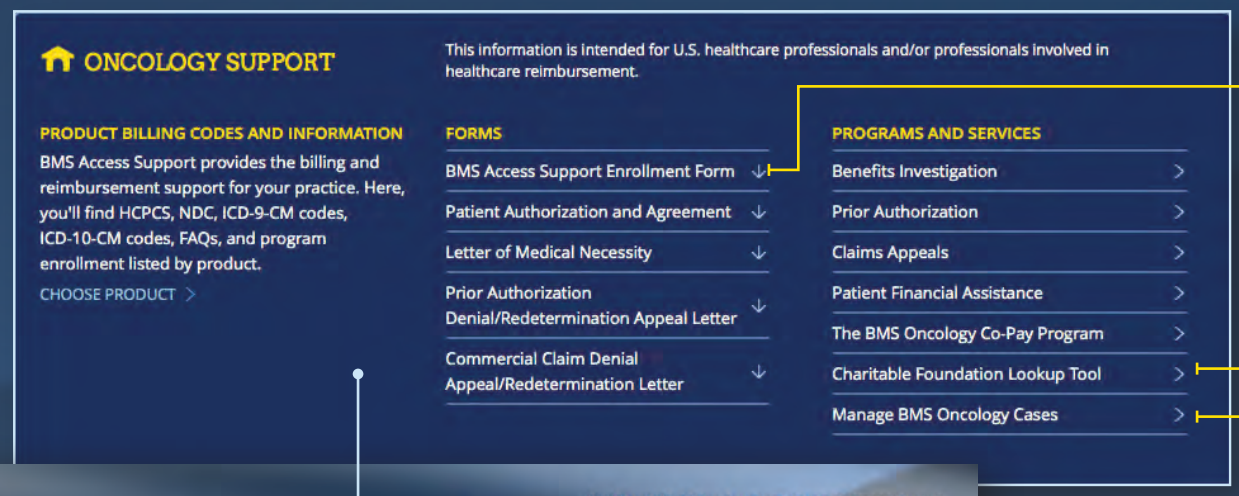

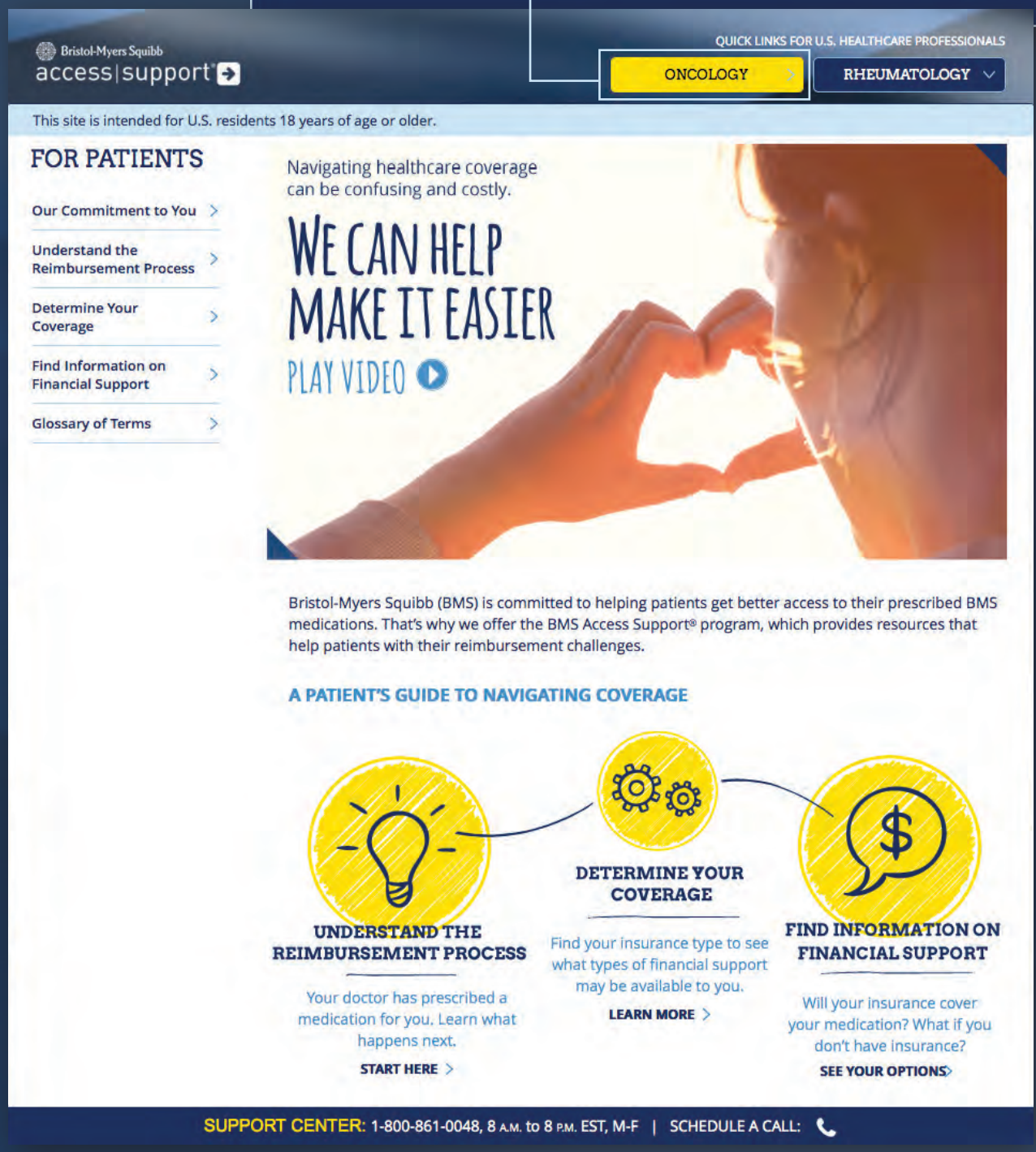

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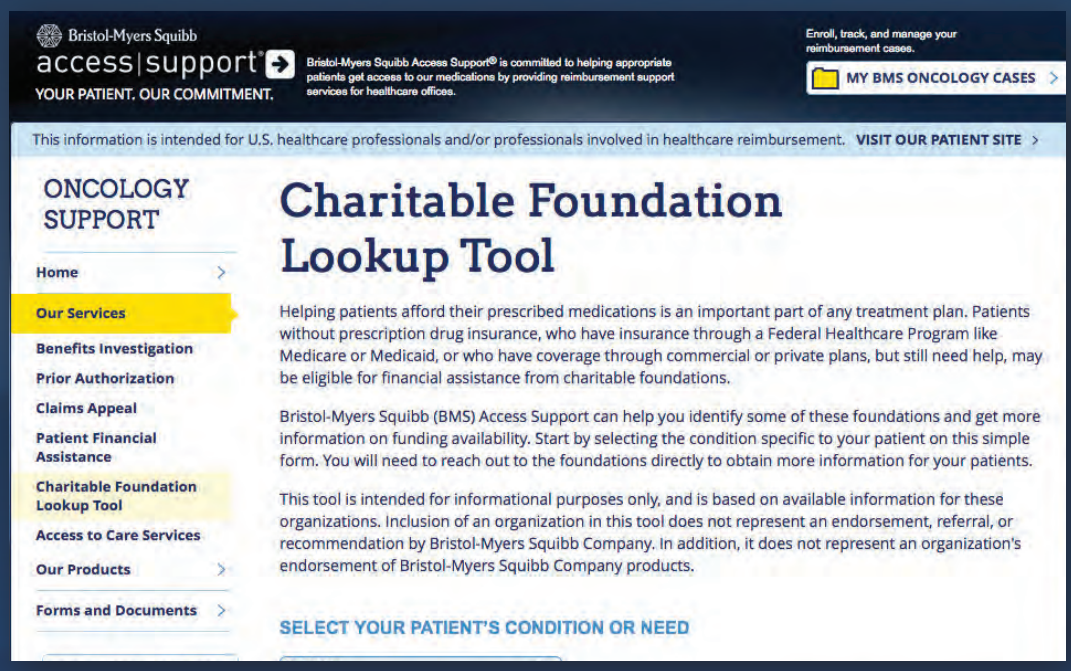

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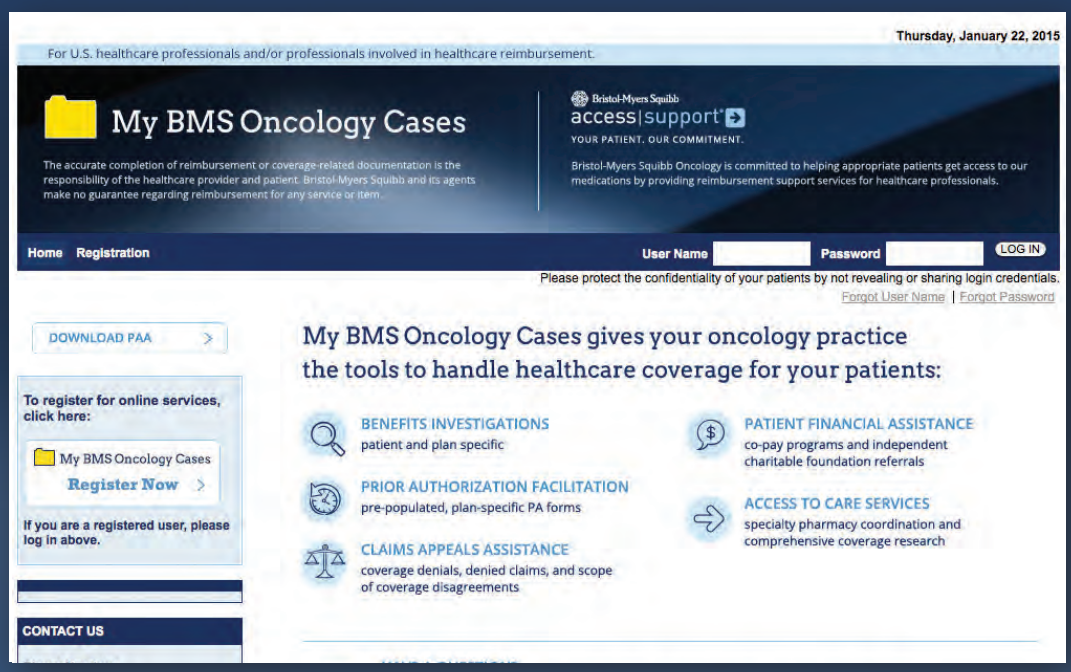

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Lisa Diller, MD, director of the David B. Perini Jr. Quality of Life Clinic for survivors of childhood cancer, provides guidance and resources to improve long-term care of pediatric cancer survivors (SP498).
Photo source: American Childhood Cancer Organization, 2015.

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Pediatric and Young Adult Cancer Care Screaming for Attention

MIKE HENNESSY, SR

Cancer incidence in the adult population in the United States has steadily been decreasing, outcomes have improved, and the number of survivors have been on the rise. Results of a report released by the American Cancer Society (ACS) last year estimated almost 14.5 million cancer survivors were living in the United States in 2014 and that this number is expected to reach 19 million over the next decade. Better and earlier screening and diagnostic tools, greater public awareness on risk factors, our deeper understanding of the disease that is cancer, which has resulted in more personalized care—progress in all of these fields has resulted in the observed improvements.

However, the picture is not as rosy with young patients who have cancer, particularly the young adult population. According to the ACS, cancer remains the leading cause of disease-related death in children and adolescents (0 to 19 years old). As has been pointed out by several of our contributors in this issue of *Evidence-Based Oncology,* the barriers are many:

- Patient access to care
- Dearth of pediatric clinical trials
- Long-term harmful effects of treatment faced by survivors
- Transition from pediatric to adult care
- Lack of psychosocial support.

In this issue, you will hear from pediatric oncologist Lisa Diller, MD, who leads the David B. Perini Jr. Quality of Life Clinic for survivors of childhood cancer at Dana-Farber Cancer Institute. Dr Diller has summarized her experience and expertise into advice for primary care physicians caring for survivors of childhood cancer. Clarke P. Anderson, MD, a pediatric oncologist at City of Hope, has, in his commentary, emphasized the importance of palliative care and psychosocial care among adolescent and young adult (AYA) cancer patients. "Strategies utilized for children or adults often miss the complex needs (eg, psychosocial changes, emerging sexuality, and existential loss of future) of the AYA," Dr Anderson writes.

Highlighting this "AYA gap," experts from the USC Norris Comprehensive Cancer Center have provided an overview of their AYA@USC program—a collaboration between pediatric and adult oncologists at the Norris Cancer Hospital and the Children's Hospital Los Angeles—which provides age-appropriate support services for young cancer patients. Future plans of the program include building a regional network to support AYA patient care.

Along with providers of care, we also hear from patients and a support group that works with patients.

Woody Roseland, an 8-time survivor, highlights the lessons learned from his cancer—and its treatment—the LIVE**STRONG** foundation shares information on organizational efforts to raise provider awareness on addressing fertility concerns of young patients and their families.

With evidence supporting cancer-related bankruptcies, AYAs are not spared of this financial burden. As the article by founders of The SAMfund suggests, although "cancer can derail the financial health of YAs, in many ways, it is their life stage that complicates their financial recovery." SAMfund helps these young adults who have survived cancer from surviving life.

We hope this issue of *EBO* contributes to raise awareness on the care needs of this unique population of patients who have cancer. Thank you for your readership.

Sincerely,

Mike Hennessy, Sr
CHAIRMAN AND CEO

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To present policy makers, payers, and providers with the clinical, pharmacoeconomic, and regulatory information they need to improve efficiency and outcomes in cancer care.

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IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage - Fatal bleeding events have occurred in patients treated with IMBRUVICA®. Grade 3 or higher bleeding events (subdural hematoma, gastrointestinal bleeding, hematuria, and post-procedural hemorrhage) have occurred in up to 6% of patients. Bleeding events of any grade, including bruising and petechiae, occurred in approximately half of patients treated with IMBRUVICA®.

The mechanism for the bleeding events is not well understood. IMBRUVICA® may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies. Consider the benefit-risk of withholding IMBRUVICA® for at least 3 to 7 days pre and post-surgery depending upon the type of surgery and the risk of bleeding.

Infections - Fatal and non-fatal infections have occurred with IMBRUVICA® therapy. Grade 3 or greater infections occurred in 14% to 26% of patients. Cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with IMBRUVICA®. Monitor patients for fever and infections and evaluate promptly.

Cytopenias - Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (range, 19 to 29%), thrombocytopenia (range, 5 to 17%), and anemia (range, 0 to 9%) occurred in patients treated with IMBRUVICA®. Monitor complete blood counts monthly.

Atrial Fibrillation - Atrial fibrillation and atrial flutter (range, 6 to 9%) have occurred in patients treated with IMBRUVICA®, particularly in patients with cardiac risk factors, acute infections, and a previous history of atrial fibrillation. Periodically monitor patients clinically for atrial fibrillation. Patients who develop arrhythmic symptoms (eg, palpitations, lightheadedness) or new-onset dyspnea should have an ECG performed. If atrial fibrillation persists, consider the risks and benefits of IMBRUVICA® treatment and dose modification.

Second Primary Malignancies - Other malignancies (range, 5 to 14%) including non-skin carcinomas (range, 1 to 3%) have occurred in patients treated with IMBRUVICA®. The most frequent second primary malignancy was non-melanoma skin cancer (range, 4 to 11%).

Tumor Lysis Syndrome - Tumor lysis syndrome has been reported with IMBRUVICA® therapy. Monitor patients closely and take appropriate precautions in patients at risk for tumor lysis syndrome (e.g. high tumor burden).

Embryo-Fetal Toxicity - Based on findings in animals, IMBRUVICA® can cause fetal harm when administered to a pregnant woman. Advise women to avoid becoming pregnant while taking IMBRUVICA®. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

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IMBRUVICA® is indicated for the treatment of patients with

Mantle cell lymphoma (MCL) who have received at least one prior therapy.
Accelerated approval was granted for this indication based on overall response rate. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials.

Chronic lymphocytic leukemia (CLL) who have received at least one prior therapy.

Chronic lymphocytic leukemia with 17p deletion.

Waldenström's macroglobulinemia (WM).

ADVERSE REACTIONS

The most common adverse reactions (≥25%) in patients with B-cell malignancies (MCL, CLL, WM) were thrombocytopenia* (57%, 52%, 43%), neutropenia* (47%, 51%, 44%), diarrhea (51%, 48%, 37%), anemia* (41%, 36%, 13%), fatigue (41%, 28%, 21%), musculoskeletal pain (37%, 28%†, NA‡), bruising (30%, 12%†, 16%†), nausea (31%, 26%, 21%), upper respiratory tract infection (34%, 16%, 19%), and rash (25%, 24%†, 22%†).

*Based on adverse reactions and/or laboratory measurements (noted as platelets, neutrophils, or hemoglobin decreased).

†Includes multiple ADR terms.

‡Not applicable; no associated ADRs.

The most common Grade 3 or 4 non-hematological adverse reactions (≥5%) in MCL patients were pneumonia (7%), abdominal pain (5%), atrial fibrillation (5%), diarrhea (5%), fatigue (5%), and skin infections (5%).

Approximately 6% (CLL), 14% (MCL), and 11% (WM) of patients had a dose reduction due to adverse events.

Approximately 5% (CLL), 9% (MCL), and 6% (WM) of patients discontinued due to adverse events. Most frequent adverse events leading to discontinuation were infections, subdural hematomas, and diarrhea in CLL patients and subdural hematoma (1.8%) in MCL patients.

DRUG INTERACTIONS

CYP3A Inhibitors - Avoid co-administration with strong and moderate CYP3A inhibitors. If a moderate CYP3A inhibitor must be used, reduce the IMBRUVICA® dose.

CYP3A Inducers - Avoid co-administration with strong CYP3A inducers.

SPECIFIC POPULATIONS

Hepatic Impairment - Avoid use in patients with moderate or severe baseline hepatic impairment. In patients with mild impairment, reduce IMBRUVICA® dose.

Please review the Brief Summary of full Prescribing Information on the following pages.

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Brief Summary of Prescribing Information for IMBRUVICA® (ibrutinib)
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See package insert for Full Prescribing Information

INDICATIONS AND USAGE

Mantle Cell Lymphoma: IMBRUVICA is indicated for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

Accelerated approval was granted for this indication based on overall response rate. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials *[see Clinical Studies (14.1) in Full Prescribing Information].*

Chronic Lymphocytic Leukemia: IMBRUVICA is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy *[see Clinical Studies (14.2) in Full Prescribing Information].*

Chronic Lymphocytic Leukemia with 17p deletion: IMBRUVICA is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL) with 17p deletion *[see Clinical Studies (14.2) in Full Prescribing Information].*

Waldenström's Macroglobulinemia: IMBRUVICA is indicated for the treatment of patients with Waldenström's macroglobulinemia (WM) *[see Clinical Studies (14.3) in Full Prescribing Information].*

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Hemorrhage: Fatal bleeding events have occurred in patients treated with IMBRUVICA. Grade 3 or higher bleeding events (subdural hematoma, gastrointestinal bleeding, hematuria and post procedural hemorrhage) have occurred in up to 6% of patients. Bleeding events of any grade, including bruising and petechiae, occurred in approximately half of patients treated with IMBRUVICA.

The mechanism for the bleeding events is not well understood.

IMBRUVICA may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies.

Consider the benefit-risk of withholding IMBRUVICA for at least 3 to 7 days pre and post-surgery depending upon the type of surgery and the risk of bleeding *[see Clinical Studies (14) in Full Prescribing Information].*

Infections: Fatal and non-fatal infections have occurred with IMBRUVICA therapy. Grade 3 or greater infections occurred in 14% to 26% of patients. *[See Adverse Reactions].* Cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with IMBRUVICA. Monitor patients for fever and infections and evaluate promptly.

Cytopenias: Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (range, 19 to 29%), thrombocytopenia (range, 5 to 17%), and anemia (range, 0 to 9%) occurred in patients treated with IMBRUVICA.

Monitor complete blood counts monthly.

Atrial Fibrillation: Atrial fibrillation and atrial flutter (range, 6 to 9%) have occurred in patients treated with IMBRUVICA, particularly in patients with cardiac risk factors, acute infections, and a previous history of atrial fibrillation. Periodically monitor patients clinically for atrial fibrillation. Patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness) or new onset dyspnea should have an ECG performed. If atrial fibrillation persists, consider the risks and benefits of IMBRUVICA treatment and dose modification *[see Dosage and Administration (2.3) in Full Prescribing Information].*

Second Primary Malignancies: Other malignancies (range, 5 to 14%) including non-skin carcinomas (range, 1 to 3%) have occurred in patients treated with IMBRUVICA. The most frequent second primary malignancy was non-melanoma skin cancer (range, 4 to 11 %).

Tumor Lysis Syndrome: Tumor lysis syndrome has been reported with IMBRUVICA therapy. Monitor patients closely and take appropriate precautions in patients at risk for tumor lysis syndrome (e.g. high tumor burden).

Embryo-Fetal Toxicity: Based on findings in animals, IMBRUVICA can cause fetal harm when administered to a pregnant woman. Ibrutinib caused malformations in rats at exposures 14 times those reported in patients with MCL and 20 times those reported in patients with CLL or WM, receiving the ibrutinib dose of 560 mg per day and 420 mg per day, respectively. Reduced fetal weights were observed at lower exposures. Advise women to avoid becoming pregnant while taking IMBRUVICA. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus *[see Use in Specific Populations].*

ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Hemorrhage *[see Warnings and Precautions]*
- Infections *[see Warnings and Precautions]*
- Cytopenias *[see Warnings and Precautions]*
- Atrial Fibrillation *[see Warnings and Precautions]*
- Second Primary Malignancies *[see Warnings and Precautions]*
- Tumor Lysis Syndrome *[see Warnings and Precautions]*

Because clinical trials are conducted under widely variable conditions, adverse event rates observed in clinical trials of a drug cannot be directly compared with rates of clinical trials of another drug and may not reflect the rates observed in practice.

Clinical Trials Experience: Mantle Cell Lymphoma: The data described below reflect exposure to IMBRUVICA in a clinical trial that included 111 patients with previously treated MCL treated with 560 mg daily with a median treatment duration of 8.3 months.

The most commonly occurring adverse reactions (≥ 20%) were thrombocytopenia, diarrhea, neutropenia, anemia, fatigue, musculoskeletal pain, peripheral edema, upper respiratory tract infection, nausea, bruising, dyspnea, constipation, rash, abdominal pain, vomiting and decreased appetite (see Tables 1 and 2).

The most common Grade 3 or 4 non-hematological adverse reactions (≥ 5%) were pneumonia, abdominal pain, atrial fibrillation, diarrhea, fatigue, and skin infections.

Fatal and serious cases of renal failure have occurred with IMBRUVICA therapy. Increases in creatinine 1.5 to 3 times the upper limit of normal occurred in 9% of patients.

Adverse reactions from the MCL trial (N=111) using single agent IMBRUVICA 560 mg daily occurring at a rate of ≥ 10% are presented in Table 1.

Table 1: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with MCL (N=111)

System Organ Class	Preferred Term	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	51	5
	Nausea	31	0
	Constipation	25	0
	Abdominal pain	24	5
	Vomiting	23	0
	Stomatitis	17	1
	Dyspepsia	11	0
Infections and infestations	Upper respiratory tract infection	34	0
	Urinary tract infection	14	3
	Pneumonia	14	7
	Skin infections	14	5
	Sinusitis	13	1
General disorders and administrative site conditions	Fatigue	41	5
	Peripheral edema	35	3
	Pyrexia	18	1
	Asthenia	14	3

Table 1: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with Mantle Cell Lymphoma (N=111) (continued)

System Organ Class	Preferred Term	All Grades (%)	Grade 3 or 4 (%)
Skin and subcutaneous tissue disorders	Bruising	30	0
	Rash	25	3
	Petechiae	11	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	37	1
	Muscle spasms	14	0
	Arthralgia	11	0
Respiratory, thoracic and mediastinal disorders	Dyspnea	27	4
	Cough	19	0
	Epistaxis	11	0
Metabolism and nutrition disorders	Decreased appetite	21	2
	Dehydration	12	4
Nervous system disorders	Dizziness	14	0
	Headache	13	0

Table 2: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with MCL (N=111)

	Percent of Patients (N=111)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	57	17
Neutrophils Decreased	47	29
Hemoglobin Decreased	41	9

* Based on laboratory measurements and adverse reactions

Ten patients (9%) discontinued treatment due to adverse reactions in the trial (N=111). The most frequent adverse reaction leading to treatment discontinuation was subdural hematoma (1.8%). Adverse reactions leading to dose reduction occurred in 14% of patients.

Patients with MCL who develop lymphocytosis greater than 400,000/mcL have developed intracranial hemorrhage, lethargy, gait instability, and headache. However, some of these cases were in the setting of disease progression.

Forty percent of patients had elevated uric acid levels on study including 13% with values above 10 mg/dL. Adverse reaction of hyperuricemia was reported for 15% of patients.

Chronic Lymphocytic Leukemia: The data described below reflect exposure to IMBRUVICA in an open label clinical trial (Study 1) that included 48 patients with previously treated CLL and a randomized clinical trial (Study 2) that included 391 randomized patients with previously treated CLL or SLL.

The most commonly occurring adverse reactions in Study 1 and Study 2 (≥ 20%) were thrombocytopenia, neutropenia, diarrhea, anemia, fatigue, musculoskeletal pain, upper respiratory tract infection, rash, nausea, and pyrexia.

Approximately five percent of patients receiving IMBRUVICA in Study 1 and Study 2 discontinued treatment due to adverse events. These included infections, subdural hematomas and diarrhea. Adverse events leading to dose reduction occurred in approximately 6% of patients.

Study 1: Adverse reactions and laboratory abnormalities from the CLL trial (N=48) using single agent IMBRUVICA 420 mg daily occurring at a rate of ≥ 10% are presented in Tables 3 and 4.

Table 3: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with CLL (N=48) in Study 1

System Organ Class	Preferred Term	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	63	4
	Constipation	23	2
	Nausea	21	2
	Stomatitis	21	0
	Vomiting	19	2
	Abdominal pain	15	0
	Dyspepsia	13	0
Infections and infestations	Upper respiratory tract infection	48	2
	Sinusitis	21	6
	Skin infection	17	6
	Pneumonia	10	8
	Urinary tract infection	10	0
General disorders and administrative site conditions	Fatigue	31	4
	Pyrexia	25	2
	Peripheral edema	23	0
	Asthenia	13	4
	Chills	13	0
Skin and subcutaneous tissue disorders	Bruising	54	2
	Rash	27	0
	Petechiae	17	0
Respiratory, thoracic and mediastinal disorders	Cough	19	0
	Oropharyngeal pain	15	0
	Dyspnea	10	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	27	6
	Arthralgia	23	0
	Muscle spasms	19	2
Nervous system disorders	Dizziness	21	0
	Headache	19	2
	Peripheral neuropathy	10	0
Metabolism and nutrition disorders	Decreased appetite	17	2
Neoplasms benign, malignant, unspecified	Second malignancies*	10*	0
Injury, poisoning and procedural complications	Laceration	10	2
Psychiatric disorders	Anxiety	10	0
	Insomnia	10	0
Vascular disorders	Hypertension	17	8

**One patient death due to histiocytic sarcoma.*

Table 4: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with CLL (N=48) in Study 1

	Percent of Patients (N=48)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	71	10
Neutrophils Decreased	54	27
Hemoglobin Decreased	44	0

* Based on laboratory measurements per IWCLL criteria and adverse reactions

Study 2: Adverse reactions and laboratory abnormalities described below in Tables 5 and 6 reflect exposure to IMBRUVICA with a median duration of 8.6 months and exposure to ofatumumab with a median of 5.3 months in Study 2.

Table 5: Non-Hematologic Adverse Reactions ≥ 10% Reported in Study 2

System Organ Class ADR Term	IMBRUVICA (N=195)		Ofatumumab (N=191)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders				
Diarrhea	48	4	18	2
Nausea	26	2	18	0
Stomatitis*	17	1	6	1
Constipation	15	0	9	0
Vomiting	14	0	6	1
General disorders and administration site conditions				
Fatigue	28	2	30	2
Pyrexia	24	2	15	1
Infections and infestations				
Upper respiratory tract infection	16	1	11	2
Pneumonia*	15	10	13	9
Sinusitis*	11	1	6	0
Urinary tract infection	10	4	5	1
Skin and subcutaneous tissue disorders				
Rash*	24	3	13	0
Petechiae	14	0	1	0
Bruising*	12	0	1	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal Pain*	28	2	18	1
Arthralgia	17	1	7	0
Nervous system disorders				
Headache	14	1	6	0
Dizziness	11	0	5	0
Injury, poisoning and procedural complications				
Contusion	11	0	3	0
Eye disorders				
Vision blurred	10	0	3	0

Subjects with multiple events for a given ADR term are counted once only for each ADR term.
The system organ class and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.
* Includes multiple ADR terms

Table 6: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Study 2

	IMBRUVICA (N=195)		Ofatumumab (N=191)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Neutrophils Decreased	51	23	57	26
Platelets Decreased	52	5	45	10
Hemoglobin Decreased	36	0	21	0

* Based on laboratory measurements per IWCLL criteria

Waldenström's Macroglobulinemia

The data described below reflect exposure to IMBRUVICA in an open label clinical trial that included 63 patients with previously treated WM.

The most commonly occurring adverse reactions in the WM trial (≥ 20%) were neutropenia, thrombocytopenia, diarrhea, rash, nausea, muscle spasms, and fatigue.

Six percent of patients receiving IMBRUVICA in the WM trial discontinued treatment due to adverse events. Adverse events leading to dose reduction occurred in 11% of patients.

Adverse reactions and laboratory abnormalities described below in Tables 7 and 8 reflect exposure to IMBRUVICA with a median duration of 11.7 months in the WM trial.

Table 7: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with Waldenström's Macroglobulinemia (N=63)

System Organ Class	Preferred Term	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	37	0
	Nausea	21	0
	Stomatitis*	16	0
	Gastroesophageal reflux disease	13	0
Skin and subcutaneous tissue disorders	Rash*	22	0
	Bruising*	16	0
	Pruritus	11	0

IMBRUVICA® (ibrutinib) capsules

Table 7: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with Waldenström's Macroglobulinemia (N=63) (continued)

System Organ Class	Preferred Term	All Grades (%)	Grade 3 or 4 (%)
General disorders and administrative site conditions	Fatigue	21	0
Musculoskeletal and connective tissue disorders	Muscle spasms	21	0
	Arthropathy	13	0
Infections and infestations	Upper respiratory tract infection	19	0
	Sinusitis	19	0
	Pneumonia*	14	6
	Skin infection*	14	2
Respiratory, thoracic and mediastinal disorders	Epistaxis	19	0
	Cough	13	0
Nervous system disorders	Dizziness	14	0
	Headache	13	0
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	Skin cancer*	11	0

The system organ class and individual ADR terms are sorted in descending frequency order.
* Includes multiple ADR terms.

Table 8: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with WM (N=63)

	Percent of Patients (N=63)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	43	13
Neutrophils Decreased	44	19
Hemoglobin Decreased	13	8

* Based on laboratory measurements.

Postmarketing Experience: The following adverse reactions have been identified during post-approval use of IMBRUVICA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hypersensitivity reactions including anaphylactic shock (fatal), urticaria, and angioedema have been reported.

DRUG INTERACTIONS

Ibrutinib is primarily metabolized by cytochrome P450 enzyme 3A.

CYP3A Inhibitors: In healthy volunteers, co-administration of ketoconazole, a strong CYP3A inhibitor, increased C_{max} and AUC of ibrutinib by 29- and 24-fold, respectively. The highest ibrutinib dose evaluated in clinical trials was 12.5 mg/kg (actual doses of 840 – 1400 mg) given for 28 days with single dose AUC values of 1445 ± 869 ng • hr/mL which is approximately 50% greater than steady state exposures seen at the highest indicated dose (560 mg).

Avoid concomitant administration of IMBRUVICA with strong or moderate inhibitors of CYP3A. For strong CYP3A inhibitors used short-term (e.g., antifungals and antibiotics for 7 days or less, e.g., ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin) consider interrupting IMBRUVICA therapy during the duration of inhibitor use. Avoid strong CYP3A inhibitors that are needed chronically. If a moderate CYP3A inhibitor must be used, reduce the IMBRUVICA dose. Patients taking concomitant strong or moderate CYP3A4 inhibitors should be monitored more closely for signs of IMBRUVICA toxicity *[see Dosage and Administration (2.4) in Full Prescribing Information].*

Avoid grapefruit and Seville oranges during IMBRUVICA treatment, as these contain moderate inhibitors of CYP3A *[see Dosage and Administration (2.4), and Clinical Pharmacology (12.3) in Full Prescribing Information].*

CYP3A Inducers: Administration of IMBRUVICA with rifampin, a strong CYP3A inducer, decreased ibrutinib C_{max} and AUC by approximately 13- and 10-fold, respectively.

Avoid concomitant use of strong CYP3A inducers (e.g., carbamazepine, rifampin, phenytoin and St. John's Wort). Consider alternative agents with less CYP3A induction *[see Clinical Pharmacology (12.3) in Full Prescribing Information].*

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy Category D *[see Warnings and Precautions].*

Risk Summary: Based on findings in animals, IMBRUVICA can cause fetal harm when administered to a pregnant woman. If IMBRUVICA is used during pregnancy or if the patient becomes pregnant while taking IMBRUVICA, the patient should be apprised of the potential hazard to the fetus.

Animal Data: Ibrutinib was administered orally to pregnant rats during the period of organogenesis at oral doses of 10, 40 and 80 mg/kg/day. Ibrutinib at a dose of 80 mg/kg/day was associated with visceral malformations (heart and major vessels) and increased post-implantation loss. The dose of 80 mg/kg/day in animals is approximately 14 times the exposure (AUC) in patients with MCL and 20 times the exposure in patients with CLL or WM administered the dose of 560 mg daily and 420 mg daily, respectively. Ibrutinib at doses of 40 mg/kg/day or greater was associated with decreased fetal weights. The dose of 40 mg/kg/day in animals is approximately 6 times the exposure (AUC) in patients with MCL administered the dose of 560 mg daily.

Nursing Mothers: It is not known whether ibrutinib is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from IMBRUVICA, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: The safety and effectiveness of IMBRUVICA in pediatric patients has not been established.

Geriatric Use: Of the 111 patients treated for MCL, 63% were 65 years of age or older. No overall differences in effectiveness were observed between these patients and younger patients. Cardiac adverse events (atrial fibrillation and hypertension), infections (pneumonia and cellulitis) and gastrointestinal events (diarrhea and dehydration) occurred more frequently among elderly patients.

Of the 391 patients randomized in Study 2, 61% were ≥ 65 years of age. No overall differences in effectiveness were observed between age groups. Grade 3 or higher adverse events occurred more frequently among elderly patients treated with IMBRUVICA (61% of patients age ≥ 65 versus 51% of younger patients) *[see Clinical Studies (14.2) in Full Prescribing Information].*

Of the 63 patients treated for WM, 59% were 65 years of age or older. No overall differences in effectiveness were observed between these patients and younger patients. Cardiac adverse events (atrial fibrillation and hypertension), and infections (pneumonia and urinary tract infection) occurred more frequently among elderly patients.

IMBRUVICA® (ibrutinib) capsules

Renal Impairment: Less than 1% of ibrutinib is excreted renally. Ibrutinib exposure is not altered in patients with Creatinine clearance (CLcr) > 25 mL/min. There are no data in patients with severe renal impairment (CLcr < 25 mL/min) or patients on dialysis *[see Clinical Pharmacology (12.3) in Full Prescribing Information].*

Hepatic Impairment: Ibrutinib is metabolized in the liver. In a hepatic impairment study, data showed an increase in ibrutinib exposure. Following single dose administration, the AUC of ibrutinib increased 2.7-, 8.2- and 9.8-fold in subjects with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment compared to subjects with normal liver function. The safety of IMBRUVICA has not been evaluated in patients with hepatic impairment.

Monitor patients for signs of IMBRUVICA toxicity and follow dose modification guidance as needed. It is not recommended to administer IMBRUVICA to patients with moderate or severe hepatic impairment (Child-Pugh classes B and C) *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3) in Full Prescribing Information].*

Females and Males of Reproductive Potential: Advise women to avoid becoming pregnant while taking IMBRUVICA because IMBRUVICA can cause fetal harm *[see Use in Specific Populations].*

Plasmapheresis: Management of hyperviscosity in patients with WM may include plasmapheresis before and during treatment with IMBRUVICA. Modifications to IMBRUVICA dosing are not required.

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information).

- *Hemorrhage:*
  Inform patients of the possibility of bleeding, and to report any signs or symptoms (blood in stools or urine, prolonged or uncontrolled bleeding). Inform the patient that IMBRUVICA may need to be interrupted for medical or dental procedures *[see Warnings and Precautions].*
- *Infections:*
  Inform patients of the possibility of serious infection, and to report any signs or symptoms (fever, chills, weakness, confusion) suggestive of infection *[see Warnings and Precautions].*
- *Atrial Fibrillation:*
  Counsel patients to report any signs of palpitations, lightheadedness, dizziness, fainting, shortness of breath, and chest discomfort *[see Warnings and Precautions].*
- *Second primary malignancies:*
  Inform patients that other malignancies have occurred in patients who have been treated with IMBRUVICA, including skin cancers and other carcinomas *[see Warnings and Precautions].*
- *Tumor lysis syndrome:*
  Inform patients of the potential risk of tumor lysis syndrome and report any signs and symptoms associated with this event to their healthcare provider for evaluation *[see Warnings and Precautions].*
- *Embryo-fetal toxicity:*
  Advise women of the potential hazard to a fetus and to avoid becoming pregnant *[see Warnings and Precautions].*
- Inform patients to take IMBRUVICA orally once daily according to their physician's instructions and that the capsules should be swallowed whole with a glass of water without being opened, broken, or chewed at approximately the same time each day *[see Dosage and Administration (2.1) in Full Prescribing Information].*
- Advise patients that in the event of a missed daily dose of IMBRUVICA, it should be taken as soon as possible on the same day with a return to the normal schedule the following day. Patients should not take extra capsules to make up the missed dose *[see Dosage and Administration (2.5) in Full Prescribing Information].*
- Advise patients of the common side effects associated with IMBRUVICA *[see Adverse Reactions].* Direct the patient to a complete list of adverse drug reactions in PATIENT INFORMATION.
- Advise patients to inform their health care providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products *[see Drug Interactions].*
- Advise patients that they may experience loose stools or diarrhea, and should contact their doctor if their diarrhea persists. Advise patients to maintain adequate hydration.

Active ingredient made in China.

Distributed and Marketed by:
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Sunnyvale, CA USA 94085
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Coordinated, Personalized Care to Improve AYA Outcomes

Over the past decade, there has been a push toward improving cancer care outcomes through the use of personalized medicine and precision medicine solutions. As researchers and clinicians have come to appreciate the extraordinary biological complexity of cancer, they have sought to develop individually tailored plans to most effectively meet patients' care needs. Much of our discussion regarding personalized medicine, however, has focused upon molecular and genomic data and the use of targeted therapeutic agents. In the rush to avail ourselves of these technology-based approaches, we have lost sight of some incredibly important opportunities to dramatically improve patient outcomes using existing technologies. One such missed opportunity is the use of age-adapted treatment strategies for adolescent and young-adult patients (AYA).

Many profound improvements in pediatric cancer survival outcomes have occurred through the use of increasingly intensive chemotherapeutic regimens. The AYA age group is defined as those patients between 15 and 39 years of age. Biologically, these patients are often healthier and better suited to receive more intensive therapeutic approaches than those used to treat older adult patients. By carefully considering AYA patients as candidates for pediatric-adapted or inspired regimens, we may be able to replicate the success of treating pediatric-aged patients in this older population.

In acute lymphoblastic leukemia (ALL), the survival outcomes for AYA patients treated with pediatric-inspired regimens are dramatically better than those of patients not receiving these therapeutic approaches. A study comparing survival outcomes between young adults treated with adult regimens on CALGB (Cancer and Leukemia Group B) trials vs those treated with pediatric regimens on CCG (Children's Cancer Group) trials found markedly superior survival among patients treated using pediatric regimens. The 6-year event-free survival rates were 64% for those patients treated using pediatric regimens vs only 38% for those treated using adult regimens.[1] Improved survival outcomes have also been demonstrated for AYA patients receiving pediatric-type treatment regimens for other types of cancer.

We have been slow to adapt to the use of AYA–appropriate regimens, and there is an opportunity gap in the number of AYA patients who receive age-appropriate therapeutic approaches.[2] As such this remains a significant, on-going disparity within the cancer care system. Some of the root causes for this disparity include lack of clinician knowledge of the need for approaching the AYA population differently, lack of provider expertise in delivering these more intensive therapeutic regimens, concerns regarding the management of treatment toxicities, and gaps in patient knowledge regarding best practice for the care of their illness.

This issue of *Evidence-Based Oncology* is focused on addressing these barriers to care. Contributors to this issue include Dr Lisa Diller, chief medical officer at the Dana-Farber/Boston Children's Cancer and Blood Disorders Center who provides guidelines on caring for AYA cancer survivors. Dr Joseph Rosenthal, chair of the Department of Pediatrics at City of Hope reviews the evidence for the use of pediatric-adapted therapeutic regimens for the care of AYA patients with ALL. Dr Clark Anderson explores the unique emotional and psychosocial issues associated with caring for this patient population.

While so much of the recent focus on improving cancer care is placed upon novel and targeted therapeutics, AYA patients may achieve significant improvements in their cure rates by making more effective use of existing technologies. By educating oncologists, hematologists, supportive care medicine providers, and the broader cancer care community on the importance of more effectively leveraging best practice for this unique patient population, we may make a profound difference in our patients' lives and their prospects for a cancer-free future. **EBO**

ABOUT THE EDITOR IN CHIEF

JOSEPH ALVARNAS, MD

Dr Alvarnas is associate clinical professor and director of medical quality and quality, risk, and regulatory management, City of Hope, Duarte, CA.

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2. Lewis DR, Seibel NL, Smith AW, Stedman MR. Adolescent and young adult cancer survival. *J Natl Cancer Inst Monogr*. 2014;49:228-235.

ZARXIO™ (filgrastim-sndz)

Subcutaneous or Intravenous Injection
300 mcg/0.5 mL | 480 mcg/0.8 mL

NOW AVAILABLE

Supported by the totality of evidence for biosimilarity and the expertise of Sandoz, a Novartis company[1,2]

- First FDA-approved biosimilar[2]
- Approved in Europe in 2009[3]
- More than 7.5 million patient-exposure days outside of the US[3]
- Confirmed biosimilarity to Neupogen® (filgrastim)[2,3]

PRODUCT ATTRIBUTE	ZARXIO[1,4]	Neupogen[4]
Identical routes of administration	✓	✓
Identical dosing schedule	✓	✓
Identical dosage strengths	✓	✓

For the ZARXIO prefilled syringe, direct administration of less than 0.3 mL is not recommended due to potential for dosing errors.

Important Safety Information

CONTRAINDICATIONS

- ZARXIO is contraindicated in patients with a history of serious allergic reactions to human granulocyte colony-stimulating factors such as filgrastim or pegfilgrastim products.

WARNINGS AND PRECAUTIONS

- Splenic rupture, including fatal cases, has been reported following the administration of filgrastim products. Patients who report left upper abdominal or shoulder pain should be evaluated.
- Acute respiratory distress syndrome (ARDS) has been reported in patients receiving filgrastim products. Patients who develop fever and lung infiltrates or respiratory distress should be evaluated. Discontinue ZARXIO in patients with ARDS.
- Serious allergic reactions, including anaphylaxis, have been reported in patients receiving filgrastim products. The majority of reported events occurred upon initial exposure. Provide symptomatic treatment for allergic reactions. Allergic reactions, including anaphylaxis, in patients receiving filgrastim products can recur within days after the discontinuation of initial anti-allergic treatment. Permanently discontinue ZARXIO in patients with serious allergic reactions.
- Sickle cell crisis, in some cases fatal, has been reported with the use of filgrastim products in patients with sickle cell trait or sickle cell disease.
- Glomerulonephritis has occurred in patients receiving filgrastim products. The diagnoses were based upon azotemia, hematuria (microscopic and macroscopic), proteinuria, and renal biopsy. Generally, events of glomerulonephritis resolved after dose reduction or discontinuation of filgrastim. If glomerulonephritis is suspected, evaluate for cause. If causality is likely, consider dose-reduction or interruption of ZARXIO.
- Alveolar hemorrhage manifesting as pulmonary infiltrates and hemoptysis requiring hospitalization have been reported in healthy donors treated with filgrastim products undergoing peripheral blood progenitor cell (PBPC) collection mobilization. Hemoptysis resolved with discontinuation of filgrastim. The use of ZARXIO for PBPC mobilization in healthy donors is not an approved indication.
- Capillary leak syndrome (CLS) has been reported after G-CSF administration, including filgrastim products, and is characterized by hypotension, hypoalbuminemia, edema and hemoconcentration. Episodes vary in frequency, severity and may be life-threatening if treatment is delayed. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive appropriate treatment.
- Confirm the diagnosis of severe chronic neutropenia (SCN) before initiating ZARXIO therapy. Myelodysplastic syndrome (MDS) and acute myelogenous leukemia (AML) have been reported to occur in the natural history of congenital neutropenia without cytokine therapy. Cytogenetic abnormalities, transformation to MDS, and AML have also been observed in patients treated with filgrastim products for SCN. Abnormal

ZARXIO™ shares the following 5 indications with Neupogen® (filgrastim)[1,4]

1 Patients with Cancer Receiving Myelosuppressive Chemotherapy

ZARXIO is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever.

2 Patients with Acute Myeloid Leukemia Receiving Induction or Consolidation Chemotherapy

ZARXIO is indicated to reduce the time to neutrophil recovery and the duration of fever following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML).

3 Patients with Cancer Undergoing Bone Marrow Transplantation

ZARXIO is indicated to reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation.

4 Patients Undergoing Autologous Peripheral Blood Progenitor Cell Collection and Therapy

ZARXIO is indicated for the mobilization of autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis.

5 Patients with Severe Chronic Neutropenia

ZARXIO is indicated for chronic administration to reduce the incidence and duration of sequelae of neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.

Important Safety Information (cont'd)

cytogenetics and MDS have been associated with the eventual development of myeloid leukemia. The effect of filgrastim products on the development of abnormal cytogenetics and the effect of continued filgrastim administration in patients with abnormal cytogenetics or MDS are unknown. If a patient with SCN develops abnormal cytogenetics or myelodysplasia, the risks and benefits of continuing ZARXIO should be carefully considered.

- Thrombocytopenia has been reported in patients receiving filgrastim products. Monitor platelet counts.
- Leukocytosis:
  - Patients with Cancer Receiving Myelosuppressive Chemotherapy: White blood cell counts of 100,000/mm^3 or greater were observed in approximately 2% of patients receiving filgrastim at dosages above 5 mcg/kg/day. In patients with cancer receiving ZARXIO as an adjunct to myelosuppressive chemotherapy, to avoid the potential risks of excessive leukocytosis, it is recommended that ZARXIO therapy be discontinued if the ANC surpasses 10,000/mm^3 after the chemotherapy-induced ANC nadir has occurred. Monitor CBCs at least twice weekly during therapy.
  - Peripheral Blood Progenitor Cell (PBPC) Collection and Therapy: During the period of administration of ZARXIO for PBPC mobilization in patients with cancer, discontinue ZARXIO if the leukocyte count rises to >100,000/mm^3.
- Cutaneous vasculitis has been reported in patients treated with filgrastim products. In most cases, the severity of cutaneous vasculitis was moderate or severe. Most of the reports involved patients with SCN receiving long-term filgrastim therapy. Hold ZARXIO therapy in patients with cutaneous vasculitis. ZARXIO may be started at a reduced dose when the symptoms resolve and the ANC has decreased.
- The possibility that filgrastim acts as a growth factor for any tumor type cannot be excluded. The safety of filgrastim products in chronic myeloid leukemia (CML) and myelodysplasia has not been established. When ZARXIO is used to mobilize PBPC, tumor cells may be released from the marrow and subsequently collected in the leukapheresis product. Available data is limited and inconclusive.
- The safety and efficacy of ZARXIO given simultaneously with cytotoxic chemotherapy have not been established. Do not use ZARXIO in the period 24 hours before through 24 hours after the administration of cytotoxic chemotherapy. The safety and efficacy of ZARXIO have not been evaluated in patients receiving concurrent radiation therapy. Avoid the simultaneous use of ZARXIO with chemotherapy and radiation therapy.
- Increased hematopoietic activity of the bone marrow in response to growth factor therapy has been associated with transient positive bone-imaging changes on nuclear imaging.

ADVERSE REACTIONS

Most common adverse reactions in patients:

- With nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs (≥5% difference in incidence compared to placebo) are thrombocytopenia, nausea, pyrexia, chest pain, pain, fatigue, back pain, arthralgia, bone pain, pain in extremity, dizziness, cough, dyspnea, rash, blood lactate dehydrogenase increased and blood alkaline phosphatase increased
- With AML (≥2% difference in incidence) are epistaxis, back pain, pain in extremity, erythema, and rash maculo-papular
- With nonmyeloid malignancies undergoing myeloablative chemotherapy followed by BMT (≥5% difference in incidence) are rash and hypersensitivity
- Undergoing peripheral blood progenitor cell mobilization and collection (≥5% incidence) are bone pain, pyrexia, blood alkaline phosphatase increased and headache
- With severe chronic neutropenia (SCN) (≥5% difference in incidence) are arthralgia, bone pain, back pain, muscle spasms, musculoskeletal pain, pain in extremity, splenomegaly, anemia, upper respiratory tract infection, urinary tract infection, epistaxis, chest pain, diarrhea, hypoesthesia, and alopecia

Please see the Brief Summary on the following pages.

References: 1. Zarxio Prescribing Information. Sandoz, Inc. August 2015. **2.** Data on file. Sandoz Inc, Princeton, NJ. **3.** US Food and Drug Administration. Christi L. Overview of the regulatory pathway and FDA's guidance for the development and approval of biosimilar products in the US (approved in European Union under the trade name Zarzio). **4.** Neupogen® Prescribing Information. Amgen, Inc. July 2015.

To report SUSPECTED ADVERSE REACTIONS, contact Sandoz Inc. at 1-800-525-8747 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

ZARX 0045 09/2015

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ZARXIO™ (filgrastim-sndz) BRIEF SUMMARY OF PRESCRIBING INFORMATION

DOSAGE AND ADMINISTRATION

Dosage in Patients with Cancer Receiving Myelosuppressive Chemotherapy or Induction and/or Consolidation Chemotherapy for AML

The recommended starting dosage of ZARXIO is 5 mcg/kg/day, administered as a single daily injection by subcutaneous injection, by short intravenous infusion (15 to 30 minutes), or by continuous intravenous infusion. Obtain a complete blood count (CBC) and platelet count before instituting ZARXIO therapy and monitor twice weekly during therapy. Consider dose escalation in increments of 5 mcg/kg for each chemotherapy cycle, according to the duration and severity of the absolute neutrophil count (ANC) nadir. Recommend stopping ZARXIO if the ANC increases beyond 10,000/mm^3 [*see Warnings and Precautions*].

Administer ZARXIO at least 24 hours after cytotoxic chemotherapy. Do not administer ZARXIO within the 24-hour period prior to chemotherapy [*see Warnings and Precautions*]. A transient increase in neutrophil count is typically seen 1 to 2 days after initiation of ZARXIO therapy. Therefore, to ensure a sustained therapeutic response, administer ZARXIO daily for up to 2 weeks or until the ANC has reached 10,000/mm^3 following the expected chemotherapy-induced neutrophil nadir. The duration of ZARXIO therapy needed to attenuate chemotherapy-induced neutropenia may be dependent on the myelosuppressive potential of the chemotherapy regimen employed.

ZARXIO prefilled syringe with BD UltraSafe Passive® Needle Guard is not designed to allow for direct administration of doses of less than 0.3 mL (180 mcg). The spring-mechanism of the needle guard apparatus affixed to the prefilled syringe interferes with the visibility of the graduation markings on the syringe barrel corresponding to 0.1mL and 0.2 mL. The visibility of these markings is necessary to accurately measure doses of ZARXIO less than 0.3 mL (180 mcg) for direct administration to patients. Thus, the direct administration to patients requiring doses of less than 0.3 mL (180 mcg) is not recommended due to the potential for dosing errors.

ZARXIO is supplied in single-dose prefilled syringes (for subcutaneous use) [*see Dosage Forms and Strengths*]. Prior to use, remove the prefilled syringe from the refrigerator and allow ZARXIO to reach room temperature for a minimum of 30 minutes and a maximum of 24 hours. Discard any prefilled syringe left at room temperature for greater than 24 hours. Visually inspect ZARXIO for particulate matter and discoloration prior to administration (the solution is clear and colorless to slightly yellowish). Do not administer ZARXIO if particulates or discoloration are observed.

Discard unused portion of ZARXIO in prefilled syringes. Do not save unused drug for later administration.

Administration Instructions for the Prefilled Syringe

Persons with latex allergies should not administer the ZARXIO prefilled syringe, because the needle cap contains natural rubber latex (derived from latex).

Dilution

If required for intraveneous administration, ZARXIO may be diluted in 5% Dextrose Injection, USP to concentrations between 5 mcg/mL and 15 mcg/ml. ZARXIO diluted to concentrations from 5 mcg/mL to 15 mcg/mL should be protected from adsorption to plastic materials by the addition of Albumin (Human) to a final concentration of 2 mg/mL. When diluted in 5% Dextrose Injection, USP, or 5% Dextrose plus Albumin (Human), ZARXIO is compatible with glass, polyvinylchloride, polyolefin, and polypropylene.

Do not dilute with saline at any time, because the product may precipitate.

Diluted ZARXIO solution can be stored at room temperature for up to 24 hours. This 24 hour time period includes the time during room temperature storage of the infusion solution and the duration of the infusion.

CONTRAINDICATIONS

ZARXIO is contraindicated in patients with a history of serious allergic reactions to human granulocyte colony-stimulating factors such as filgrastim or pegfilgrastim products

WARNINGS AND PRECAUTIONS

Splenic Rupture

Splenic rupture, including fatal cases, has been reported following the administration of filgrastim products. Evaluate patients who report left upper abdominal or shoulder pain for an enlarged spleen or splenic rupture.

Acute Respiratory Distress Syndrome (ARDS)

Acute respiratory distress syndrome (ARDS) has been reported in patients receiving filgrastim products. Evaluate patients who develop fever and lung infiltrates or respiratory distress for ARDS. Discontinue ZARXIO in patients with ARDS.

Serious Allergic Reactions

Serious allergic reactions, including anaphylaxis, have been reported in patients receiving filgrastim products. The majority of reported events occurred upon initial exposure. Provide symptomatic treatment for allergic reactions. Allergic reactions, including anaphylaxis, in patients receiving filgrastim products can recur within days after the discontinuation of initial anti-allergic treatment. Permanently discontinue ZARXIO in patients with serious allergic reactions. ZARXIO is contraindicated in patients with a history of serious allergic reactions to human granulocyte colony-stimulating factors such as filgrastim or pegfilgrastim products.

Sickle Cell Disorders

Sickle cell crisis, in some cases fatal, has been reported with the use of filgrastim products in patients with sickle cell trait or sickle cell disease.

Glomerulonephritis

Glomerulonephritis has occurred in patients receiving filgrastim. The diagnoses were based upon azotemia, hematuria (microscopic and macroscopic), proteinuria, and renal biopsy. Generally, events of glomerulonephritis resolved after dose reduction or discontinuation of filgrastim. If glomerulonephritis is suspected, evaluate for cause. If causality is likely, consider dose-reduction or interruption of ZARXIO.

Alveolar Hemorrhage and Hemoptysis

Alveolar hemorrhage manifesting as pulmonary infiltrates and hemoptysis requiring hospitalization have been reported in healthy donors treated with filgrastim products undergoing peripheral blood progenitor cell (PBPC) collection mobilization. Hemoptysis resolved with discontinuation of filgrastim. The use of ZARXIO for PBPC mobilization in healthy donors is not an approved indication.

Capillary Leak Syndrome

Capillary leak syndrome (CLS) has been reported after G-CSF administration, including filgrastim products, and is characterized by hypotension, hypoalbuminemia, edema and hemoconcentration. Episodes vary in frequency, severity and may be life-threatening if treatment is delayed. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care.

Patients with Severe Chronic Neutropenia

Confirm the diagnosis of SCN before initiating ZARXIO therapy. Myelodysplastic syndrome (MDS) and acute myelogenous leukemia (AML) have been reported to occur in the natural history of congenital neutropenia without cytokine therapy. Cytogenetic abnormalities, transformation to MDS, and AML have also been observed in patients treated with filgrastim products for SCN. Based on available data including a postmarketing surveillance study, the risk of developing MDS and AML appears to be confined to the subset of patients with congenital neutropenia. Abnormal cytogenetics and MDS have been associated with the eventual development of myeloid leukemia. The effect of filgrastim products on the development of abnormal cytogenetics and the effect of continued filgrastim administration in patients with abnormal cytogenetics or MDS are unknown. If a patient with SCN develops abnormal cytogenetics or myelodysplasia, the risks and benefits of continuing ZARXIO should be carefully considered.

Thrombocytopenia

Thrombocytopenia has been reported in patients receiving filgrastim products. Monitor platelet counts.

Leukocytosis

Patients with Cancer Receiving Myelosuppressive Chemotherapy

White blood cell counts of 100,000/mm^3 or greater were observed in approximately 2% of patients receiving filgrastim at dosages above 5 mcg/kg/day. In patients with cancer receiving ZARXIO as an adjunct to myelosuppressive chemotherapy, to avoid the potential risks of excessive leukocytosis, it is recommended that ZARXIO therapy be discontinued if the ANC surpasses 10,000/mm^3 after the chemotherapy-induced ANC nadir has occurred. Monitor CBCs at least twice weekly during therapy [*see Warnings and Precautions*]. Dosages of ZARXIO that increase the ANC beyond 10,000/mm^3 may not result in any additional clinical benefit. In patients with cancer receiving myelosuppressive chemotherapy, discontinuation of filgrastim therapy usually resulted in a 50% decrease in circulating neutrophils within 1 to 2 days, with a return to pretreatment levels in 1 to 7 days.

Peripheral Blood Progenitor Cell Collection and Therapy

During the period of administration of ZARXIO for PBPC mobilization in patients with cancer, discontinue ZARXIO if the leukocyte count rises to $>$ 100,000/mm^3.

Cutaneous Vasculitis

Cutaneous vasculitis has been reported in patients treated with filgrastim products. In most cases, the severity of cutaneous vasculitis was moderate or severe. Most of the reports involved patients with SCN receiving long-term filgrastim therapy. Hold ZARXIO therapy in patients with cutaneous vasculitis. ZARXIO may be started at a reduced dose when the symptoms resolve and the ANC has decreased.

Potential Effect on Malignant Cells

ZARXIO is a growth factor that primarily stimulates neutrophils. The granulocyte-colony stimulating factor (G-CSF) receptor through which ZARXIO acts has also been found on tumor cell lines. The possibility that ZARXIO acts as a growth factor for any tumor type cannot be excluded. The safety of filgrastim products in chronic myeloid leukemia (CML) and myelodysplasia has not been established. When ZARXIO is used to mobilize PBPC, tumor cells may be released from the marrow and subsequently collected in the leukapheresis product. The effect of reinfusion of tumor cells has not been well studied, and the limited data available are inconclusive.

Simultaneous Use with Chemotherapy and Radiation Therapy Not Recommended

The safety and efficacy of ZARXIO given simultaneously with cytotoxic chemotherapy have not been established. Because of the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy, do not use ZARXIO in the period 24 hours before through 24 hours after the administration of cytotoxic chemotherapy [*see Dosage and Administration*].

The safety and efficacy of ZARXIO have not been evaluated in patients receiving concurrent radiation therapy. Avoid the simultaneous use of ZARXIO with chemotherapy and radiation therapy.

Nuclear Imaging

Increased hematopoietic activity of the bone marrow in response to growth factor therapy has been associated with transient positive bone-imaging changes. This should be considered when interpreting bone-imaging results.

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Adverse Reactions in Patients with Cancer Receiving Myelosuppressive Chemotherapy

The following adverse reaction data in Table 2 are from three randomized, placebo-controlled studies in patients with:

- small cell lung cancer receiving standard dose chemotherapy with cyclophosphamide, doxorubicin, and etoposide (Study 1)
- small cell lung cancer receiving ifosfamide, doxorubicin, and etoposide (Study 2), and
- non-Hodgkin's lymphoma (NHL) receiving doxorubicin, cyclophosphamide, vindesine, bleomycin, methylprednisolone, and methotrexate ("ACVBP") or mitoxantrone, ifosfamide, mitoguazone, teniposide, methotrexate, folinic acid, methylprednisolone, and methotrexate ("VIM3") (Study 3).

A total of 451 patients were randomized to receive subcutaneous filgrastim 230 mcg/m^2 (Study 1), 240 mcg/m^2 (Study 2) or 4 or 5 mcg/kg/day (Study 3) (n = 294) or placebo (n = 157). The patients in these studies were median age 61 (range 29 to 78) years and 64% were male. The ethnicity was 95% Caucasian, 4% African American, and 1% Asian.

Adverse Reactions in Patients with Cancer Receiving Myelosuppressive Chemotherapy (With ≥ 5% Higher Incidence in Filgrastim Compared to Placebo)

System Organ Class Preferred Term	**Filgrastim (N = 294)**	**Placebo (N = 157)**
Blood and lymphatic system disorders		
Thrombocytopenia	38%	29%
Gastrointestinal disorders		
Nausea	43%	32%
General disorders and administration site conditions		
Pyrexia	48%	29%
Chest pain	13%	6%
Pain	12%	6%
Fatigue	20%	10%
Musculoskeletal and connective tissue disorders		
Back pain	15%	8%
Arthralgia	9%	2%
Bone pain	11%	6%
Pain in extremity*	7%	3%
Nervous system disorders		
Dizziness	14%	3%
Respiratory, thoracic and mediastinal disorders		
Cough	14%	8%
Dyspnea	13%	8%
Skin and subcutaneous tissue disorders		
Rash	14%	5%
Investigations		
Blood lactate dehydrogenase increased	6%	1%
Blood alkaline phosphatase increased	6%	1%

*Percent difference (Filgrastim – Placebo) was 4%.

Adverse events with ≥ 5% higher incidence in filgrastim patients compared to placebo and associated with the sequelae of the underlying malignancy or cytotoxic chemotherapy delivered included anemia, constipation, diarrhea, oral pain, vomiting, asthenia, malaise, edema peripheral, hemoglobin decreased, decreased appetite, oropharyngeal pain, and alopecia.

Adverse Reactions in Patients with Acute Myeloid Leukemia

Adverse reaction data below are from a randomized, double-blind, placebo-controlled study in patients with AML (Study 4) who received an induction chemotherapy regimen of intravenous daunorubicin days 1, 2, and 3; cytosine arabinoside days 1 to 7; and etoposide days 1 to 5 and up to 3 additional courses of therapy (induction 2, and consolidation 1, 2) of intravenous daunorubicin, cytosine arabinoside, and etoposide. The safety population included 518 patients randomized to receive either 5 mcg/kg/day filgrastim (n = 257) or placebo (n = 261). The median age was 54 (range 16 to 89) years and 54% were male.

Adverse reactions with ≥ 2% higher incidence in filgrastim patients compared to placebo included epistaxis, back pain, pain in extremity, erythema, and rash maculo-papular.

Adverse events with ≥ 2% higher incidence in filgrastim patients compared to placebo and associated with the sequelae of the underlying malignancy or cytotoxic chemotherapy included diarrhea, constipation, and transfusion reaction.

Adverse Reactions in Patients with Cancer Undergoing Bone Marrow Transplantation

The following adverse reaction data are from one randomized, no treatment-controlled study in patients with acute lymphoblastic leukemia or lymphoblastic lymphoma receiving high-dose chemotherapy (cyclophosphamide or cytarabine, and melphalan) and total body irradiation (Study 5) and one randomized, no treatment controlled study in patients with Hodgkin's disease (HD) and NHL undergoing high-dose chemotherapy and autologous bone marrow transplantation (Study 6). Patients receiving autologous bone marrow transplantation only were included in the analysis. A total of 100 patients received either 30 mcg/kg/day as a 4 hour infusion (Study 5) or 10 mcg/kg/day or 30 mcg/kg/day as a 24 hour infusion (Study 6) filgrastim (n = 72), no treatment control or placebo (n = 28). The median age was 30 (range 15 to 57) years, 57% were male.

Adverse reactions with ≥ 5% higher incidence in filgrastim patients compared to patients receiving no filgrastim included rash and hypersensitivity.

Adverse reactions in patients receiving intensive chemotherapy followed by autologous BMT with ≥ 5% higher incidence in filgrastim patients compared to patients receiving no filgrastim included thrombocytopenia, anemia, hypertension, sepsis, bronchitis, and insomnia.

Adverse Reactions in Patients with Cancer Undergoing Autologous Peripheral Blood Progenitor Cell Collection

The adverse reaction data in Table 3 are from a series of 7 trials in patients with cancer undergoing mobilization of autologous peripheral blood progenitor cells for collection by leukapheresis. Patients (n = 166) in all these trials underwent a similar mobilization/collection regimen: filgrastim was administered for 6 to 8 days, in most cases the apheresis procedure occurred on days 5, 6, and 7. The dosage of filgrastim ranged between 5 to 30 mcg/kg/day and was administered subcutaneously by injection or continuous infusion. The median age was 39 (range 15 to 67) years, and 48% were male.

Adverse Reactions in Patients with Cancer Undergoing Autologous PBPC in the Mobilization Phase (≥ 5% Incidence in Filgrastim Patients)

System Organ Class Preferred Term	**Mobilization Phase (N = 166)**
Musculoskeletal and connective tissue disorders	
Bone pain	30%
General disorders and administration site conditions	
Pyrexia	16%
Investigations	
Blood alkaline phosphatase increased	11%
Nervous system disorders	
Headache	10%

Adverse Reactions in Patients with Severe Chronic Neutropenia

The following adverse reaction data were identified in a randomized, controlled study in patients with SCN receiving filgrastim (Study 7). 123 patients were randomized to a 4 month observation period followed by subcutaneous filgrastim treatment or immediate subcutaneous filgrastim treatment. The median age was 12 years (range 7 months to 76 years) and 46% were male. The dosage of filgrastim was determined by the category of neutropenia.

Initial dosage of filgrastim:

- Idiopathic neutropenia: 3.6 mcg/kg/day
- Cyclic neutropenia: 6 mcg/kg/day
- Congenital neutropenia: 6 mcg/kg/day divided 2 times per day

The dosage was increased incrementally to 12 mcg/kg/day divided 2 times per day if there was no response. Adverse reactions with ≥ 5% higher incidence in filgrastim patients compared to patients receiving no filgrastim included arthralgia, bone pain, back pain, muscle spasms, musculoskeletal pain, pain in extremity, splenomegaly, anemia, upper respiratory tract infection, and urinary tract infection (upper respiratory

tract infection and urinary tract infection were higher in the filgrastim arm, total infection related events were lower in filgrastim treated patients), epistaxis, chest pain, diarrhea, hypoesthesia, and alopecia.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The incidence of antibody development in patients receiving filgrastim has not been adequately determined. While available data suggest that a small proportion of patients developed binding antibodies to filgrastim, the nature and specificity of these antibodies has not been adequately studied. In clinical studies using filgrastim, the incidence of antibodies binding to filgrastim was 3% (11/333). In these 11 patients, no evidence of a neutralizing response was observed using a cell-based bioassay. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay, and the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, timing of sampling, sample handling, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to filgrastim reported in this section with the incidence of antibodies in other studies or to other filgrastim products may be misleading.

Cytopenias resulting from an antibody response to exogenous growth factors have been reported on rare occasions in patients treated with other recombinant growth factors.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. The potential risk to the fetus is unknown. Reports in the scientific literature have described transplacental passage of filgrastim products in pregnant women when administered ≤ 30 hours prior to preterm delivery (≤ 30 weeks gestation). ZARXIO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Effects of filgrastim on prenatal development have been studied in rats and rabbits. No malformations were observed in either species. Filgrastim has been shown to have adverse effects in pregnant rabbits at doses 2 to 10 times higher than the human doses. In pregnant rabbits showing signs of maternal toxicity, reduced embryo-fetal survival (at 20 and 80 mcg/kg/day) and increased abortions (at 80 mcg/kg/day) were observed. In pregnant rats, no maternal or fetal effects were observed at doses up to 575 mcg/kg/day.

Offspring of rats administered filgrastim during the peri-natal and lactation periods exhibited a delay in external differentiation and growth retardation (≥ 20 mcg/kg/day) and slightly reduced survival rate (100 mcg/kg/day).

Nursing Mothers

It is not known whether filgrastim products are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if ZARXIO is administered to women who are breastfeeding.

Pediatric Use

ZARXIO prefilled syringe with BD UltraSafe Passive™ Needle Guard may not accurately measure volumes less than 0.3 mL due to the needle spring mechanism design. Therefore, the direct administration of a volume less than 0.3 mL is not recommended due to the potential for dosing errors.

In patients with cancer receiving myelosuppressive chemotherapy, 15 pediatric patients median age 2.6 (range 1.2 – 9.4) years with neuroblastoma were treated with myelosuppressive chemotherapy (cyclophosphamide, cisplatin, doxorubicin, and etoposide) followed by subcutaneous filgrastim at doses of 5, 10, or 15 mcg/kg/day for 10 days (n = 5/dose) (Study 8). The pharmacokinetics of filgrastim in pediatric patients after chemotherapy are similar to those in adults receiving the same weight-normalized doses, suggesting no age-related differences in the pharmacokinetics of filgrastim. In this population, filgrastim was well tolerated. There was one report of palpable splenomegaly and one report of hepatosplenomegaly associated with filgrastim therapy; however, the only consistently reported adverse event was musculoskeletal pain, which is no different from the experience in the adult population.

The safety and effectiveness of filgrastim have been established in pediatric patients with SCN [*see Clinical Studies*]. In a phase 3 study (Study 7) to assess the safety and efficacy of filgrastim in the treatment of SCN, 123 patients with a median age of 12 years (range 7 months to 76 years) were studied. Of the 123 patients, 12 were infants (7 months to 2 years of age), 49 were children (2 to 12 years of age), and 9 were adolescents (12 to 16 years of age). Additional information is available from a SCN postmarketing surveillance study, which includes long-term follow-up of patients in the clinical studies and information from additional patients who entered directly into the postmarketing surveillance study. Of the 731 patients in the surveillance study, 429 were pediatric patients < 18 years of age (range 0.9 -17) [*see Indications and Usage, Dosage and Administration, and Clinical Studies*].

Long-term follow-up data from the postmarketing surveillance study suggest that height and weight are not adversely affected in patients who received up to 5 years of filgrastim treatment. Limited data from patients who were followed in the phase 3 study for 1.5 years did not suggest alterations in sexual maturation or endocrine function.

Pediatric patients with congenital types of neutropenia (Kostmann's syndrome, congenital agranulocytosis, or Schwachman-Diamond syndrome) have developed cytogenetic abnormalities and have undergone transformation to MDS and AML while receiving chronic filgrastim treatment. The relationship of these events to filgrastim administration is unknown [*see Warnings and Precautions, Adverse Reactions*].

Geriatric Use

Among 855 subjects enrolled in 3 randomized, placebo-controlled trials of filgrastim treated-patients receiving myelosuppressive chemotherapy, there were 232 subjects age 65 or older, and 22 subjects age 75 or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Clinical studies of filgrastim in other approved indications (i.e., BMT recipients, PBPC mobilization, and SCN) did not include sufficient numbers of subjects aged 65 and older to determine whether elderly subjects respond differently from younger subjects.

OVERDOSAGE

The maximum tolerated dose of filgrastim products has not been determined. In filgrastim clinical trials of patients with cancer receiving myelosuppressive chemotherapy, WBC counts > 100,000/mm^3 have been reported in less than 5% of patients, but were not associated with any reported adverse clinical effects. Patients in the BMT studies received up to 138 mcg/kg/day without toxic effects, although there was a flattening of the dose response curve above daily doses of greater than 10 mcg/kg/day.

Pharmacokinetics

Specific Populations

The pharmacokinetics of filgrastim were studied in pediatric patients with advanced neuroblastoma [*see Use in Specific Populations*], in subjects with renal impairment, and in subjects with hepatic impairment.

Pediatric Patients: The pharmacokinetics of filgrastim in pediatric patients after chemotherapy are similar to those in adults receiving the same weight-normalized doses, suggesting no age-related differences in the pharmacokinetics of filgrastim products.

Renal Impairment: In a study with healthy volunteers, subjects with moderate renal impairment, and subjects with end stage renal disease (n=4 per group), higher serum concentrations were observed in subjects with end-stage renal disease. However, dose adjustment in patients with renal impairment is not necessary.

Hepatic Impairment: Pharmacokinetics and pharmacodynamics of filgrastim are similar between subjects with hepatic impairment and healthy subjects (n = 12/group). The study included 10 subjects with mild hepatic impairment (Child-Pugh Class A) and 2 subjects with moderate hepatic impairment (Child-Pugh Class B). Therefore, dose adjustment for ZARXIO in patients with hepatic impairment is not necessary.

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The Need to Raise Awareness for Young Adult Cancer Care

SURABHI DANGI-GARIMELLA, PHD

According to the National Cancer Institute (NCI), although the 5-year survival rates of children with cancers has improved dramatically over the years—from 10% a half-century ago to 80% today—survival in the adolescent and young adult (AYA) population has not seen much progress. The 5-year survival rate for AYA patients has stagnated at 70% over the last 30 years.[1] These statistics highlight the progress seen in pediatric cancer research, in contrast with the lack of similar advances in AYA research.

One of the barriers to progress in the field of AYA research has been the low enrollment rates in clinical trials observed with the adolescent (15 to 19 years) population. Whereas more than 90% of younger children diagnosed with cancer participate in clinical trials, percentages range between 5% and 34% for the adolescent population. To help identify and resolve some of these issues, the CDC's Division of Cancer Prevention and Control convened a workgroup in 2014.[2] The workgroup identified the following issues with trial enrollment among AYA patients with cancer:

- Low referral rates of adolescent patients with cancer to pediatric cancer centers
- Limited availability of clinical trials for certain cancers
- Physician-related barriers limiting clinical trial accrual
- Institutional barriers impeding collaboration between pediatric and adult oncologists on clinical trials
- Unique psychosocial needs of adolescent patients with cancer.[2]

One of these challenges—the lack of trials for certain cancers—could be resolved if the pediatric version of the NCI-Molecular Analysis for Therapy Choice (NCI-MATCH) is approved for launch in 2016. The trial design for NCI-MATCH, the adult version of which initiated enrollment in August 2015, analyzes patient tumors for actionable mutations for which a drug already exists. The idea is to target the molecular abnormality rather than the tumor type. The pediatric MATCH, to be led by the Children's Oncology Group, expects to enroll children with advanced cancers who have progressed on standard therapy and have few other therapeutic options.[3] Rajen Mody, MBBS, a pediatric oncologist at the University of Michigan who spoke with *Evidence-Based Oncology* (see page **SP498**), is one of the clinicians participating in NCI-MATCH.

Photo source: stupidcancer.org.

CHALLENGES WITH CARE TRANSITIONS

An important aspect of AYA cancer care—a fact that resonates with several contributors in this issue of *Evidence-Based Oncology*—is the challenge presented by the age of the YA patients. The physiologic and psychosocial changes that accompany a child's transition into adulthood can be traumatic enough for a teenager. When they suffer from cancer, however, the disease and its associated treatment sometimes requires these patients to place their "normal" life on the back burner, which can further fuel the emotional upheaval.

Additionally, medical challenges associated with transitioning AYAs from pediatric oncology care to adult-focused care are many, the most important being educating both survivors and providers on the long-term health risks that cancer treatment brings. Several cancer centers have long-term follow-up (LTFU) programs to assist with the transition. The LTFU programs not only cater to the needs of survivors and their families, but also assist specialists of adult medicine who lack the knowledge or skills to care for these complex patients.[4]

However, there's often a disconnect among the pediatric oncologist, the survivor, and the primary or specialty care providers that survivors see outside of oncology. These barriers could be associated with the health system (eg, care policies or medical insurance), the healthcare provider (eg, knowledge of late effects, core beliefs in prevention, or organizational structure of the clinical practice), or the survivor (eg, psychological factors, risk awareness, spiritual beliefs).

Disease-specific models have been developed and tested that include a transition team of subspecialists in pediatric and adult medicine; their role is to bridge the pediatric team and the adult medicine team. The following are elements of a suitable transition and transfer plan for a YA cancer survivor:

- **BEFORE THE VISIT:**
  - initial data collection
  - core team meeting
- **CLINIC VISIT:**
  - introduction of program concepts
  - history and physical examination
  - participation of trainees
  - patient education
  - modification of patient care plan
  - appropriate therapeutic intervention
  - referrals as needed
- **AFTER THE CLINIC VISIT:**
  - review of all available data on the patient
  - finalize patient care plan and long-term care plan
  - communication with associated care providers, patient, and family
- **ONGOING:**
  - Web-based education system for care providers
  - clinical research studies
  - educating care providers
  - support groups for survivors and families
  - develop protocols for long-term follow-up of pediatric cancer survivors.[5]

INSURANCE WOES

Insurance coverage for YAs who have survived the medical trauma is another challenge. Having spent a lot of their time fighting the disease and then readjusting to their daily routine, these individuals are likely to have interrupted their education or to have seen a career halt. Two-thirds of pediatric cancer survivors develop a chronic medical condition. However, less than half of adult survivors who were a part of the longitudinal cohort of the Childhood Cancer Survivor Study received a cancer-related visit during a 2-year study period. Further, those without insurance were, not surprisingly, at the greatest risk of inadequate follow-up.[6]

Fortunately, the Affordable Care Act enacted in 2010 has provisions to broaden coverage that could be relevant for pediatric cancer survivors. The following specific provisions could particularly help YA survivors of pediatric cancer:

- Prohibition of discrimination on the basis of health status (no denial or cancellation of coverage for newly developed or preexisiting conditions)
- Coverage on parent's insurance (through age 26 years on parents' private insurance)
- Change in minimum income eligibility for Medicaid (states can raise eligibility to 133% of the federal poverty line)
- No annual or lifetime coverage limits
- State-based exchanges (qualifying individuals can receive subsidies).[6]

According to Archie Bleyer, MD, a pediatric oncologist at Oregon Health and Science University, "We need to rethink and develop a new discipline of young doctors who can take care of adolescents and young adults. And we, as a society, have to overcome the idea of someone turning 18 and suddenly becoming an adult. This artificiality is also hurting medicine."[7] **EBO**

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Treatment of Acute Lymphoblastic Leukemia in Adolescents and Young Adults

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Although overall cancer survival rates among pediatric and older adult patients have increased in recent decades, survival of AYA patients with cancer has seen little improvement since 1975 when collected data became adequate to evaluate this issue.

ADOLESCENTS AND YOUNG ADULTS CONSTITUTES A DISTINCT GROUP IN ONCOLOGY

Adolescents and young adults (AYAs) with cancer have been recognized as a distinct subgroup of patients in the field of oncology since 2006. From the onset of symptoms until the completion of active therapy and beyond, the particular challenges this group faces have been overlooked and underestimated.

In 2006, it was noted that improvements in cancer outcomes observed for the US population as a whole had not been experienced by AYA patients.[1] The reduction in the cancer mortality rate in this group has lagged behind the reduction noted in children and older adults. As a result, although AYAs with cancer had a relatively better prognosis a quarter of a century ago, compared with children with cancer, that advantage has now been lost.

AYA patients comprise a complex and diverse group with various levels of developmental maturity—and, consequently, unique and largely unmet clinical and psychosocial needs.[2-4] Each year, nearly 70,000 individuals aged 15 to 40 years are diagnosed with cancer in the United States. Although overall cancer survival rates among pediatric and older adult patients have increased in recent decades, survival of AYA patients with cancer has seen little improvement since 1975 when collected data became adequate to evaluate this issue. In 2006, the National Cancer Institute and the Lance Armstrong Foundation (now the Livestrong Foundation) conducted a program review group of the AYA problem. Recommendations covered awareness, prevention/cancer control/epidemiology/risk, biology, access, health insurance, clinical care models, clinical trials/research, special populations, psychosocial and behavioral factors, health-related quality of life, and long-term effects.[2-4]

ACUTE LYMPHOBLASTIC LEUKEMIA IN AYA

Acute lymphoblastic leukemia (ALL) is one of the leading causes of cancer-related deaths among AYAs. Overall survival and disease-specific survival of ALL are clinically significantly poorer in AYA patients than in children aged 1 to 10 years. It is not known whether this difference in outcomes is due to distinct genetic and biological features, different therapeutic regimens and intensities, differences in compliance to therapy, or other social and behavioral issues. AYAs (16 to 21 years of age) with ALL have worse outcomes (7-year event-free survival [EFS] = 34%) than children between 1 and 10 years of age for whom the cure rate now approaches 80% to 85%.

PEDIATRIC-INSPIRED VERSUS STANDARD "ADULT" ALL PROTOCOLS

Several retrospective studies that focused on younger AYA patients (15 to 21 years old) reported that AYAs treated with standard adult protocols (SAPs) for ALL had unfavorable outcomes compared with similarly aged patients treated with pediatric-inspired protocols (PIPs). A large retrospective study reported on a comparison of presenting features, planned treatment, complete remission (CR) rate, and outcome of 321 AYAs aged 16 to 20 years with newly diagnosed ALL who were treated in consecutive trials in either the Children's Cancer Group (CCG) or the Cancer and Leukemia Group B (CALGB). The CR rates were identical: 90% for CALGB and CCG AYAs. However, CCG AYAs had a 63% EFS and 67% overall survival (OS) at 7 years in contrast to the CALGB AYAs, among whom the 7-year EFS was 34% (P <.001; relative hazard rate [RHR] = 2.2) and OS was 46% (P <.001; RHR = 1.9). Comparison of the regimens showed that AYA patients treated on the CCG regimen received earlier and more intensive central nervous system prophylaxis and higher cumulative doses of non-myelosuppressive agents. There were no differences in outcomes of those who reached maintenance therapy on time compared with those who were delayed.[5] Similar results have been observed in retrospective analyses of AYA patients in France,[6] the United Kingdom,[7] the Netherlands,[8] and Japan[9] (TABLE 1).

The most widely used regimen in adults with ALL is hyper-CVAD, consisting of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, developed at MD Anderson Cancer Center in Houston.[10,11] A prospective cohort of AYA patients treated along the guidelines of a pediatric regimen, the augmented Berlin-Frankfurt-Munster (ABFM), was compared with a retrospective cohort of similar population treated with the hyper-CVAD regimen. The 3-year complete remission duration (CRD) and OS rates were similar between the groups (TABLE 1). Severe regimen toxicities included transient hepatotoxicity in 35% to 39% of patients and pancreatitis in 11% of patients that were closely related to the use of asparaginase in the regimen. Other toxicities included osteonecrosis in 11% of patients and thrombosis in 22% of patients, which were similar to those reported with the hyper-CVAD regimen.[12]

Similar outcomes comparing SAP and PIP ALL regimens were reported in a prospective study from Finland. No significant differences were observed between AYAs treated on a PIP regimen and those treated on a SAP.[13] Although reasons for the differences noted in a majority of the reports[5-8,14] are unclear, possible hypothetical explanations include potential clinical and biological differences among AYAs compared with adults, differences in protocol design and dose intensity, and potential variations in the degree of adherence to the treatment regimens administered by medical oncologists compared with pediatric oncologists.

To address many of these unanswered questions, the adult cooperative groups have performed a large prospective trial that focuses specifically on AYAs (Intergroup trial C10403).[15] Newly diagnosed ALL patients aged 16 to 40 years were eligible for treatment that parallels the current Children Oncology Group (COG) study (AALL0232)[10] consisting of 4 intensive courses: remission induction, remission consolidation, interim maintenance, and delayed intensification, followed by prolonged maintenance therapy (TABLE 2). The results show that of the 318 patients enrolled on the trial, 22 withdrew prior to therapy. The median age at diagnosis was 24 years (range: 17 to 39 years). Patients were stratified into 3 age groups: 25% were 17 to 20 years, 53% were 21 to 29 years, and 22% were 30 to 39 years. The majority had B-ALL (76%) and were male (61%).

Overall, treatment toxicities were similar to those reported in the standard arm of COG AALL0232, with an increased thrombosis and early hyperbilirubinemia observed in C10403 patients. The median EFS overall is 59.4 months (95% confidence interval (CI), 0.384 to not releasable) and the 2-year EFS rate overall was 66% (95% CI, 0.60-0.72), with similar 2-year EFS rates for B and T-ALL patients (65% and 68%, respectively). The 2-year OS rate was 78% (95% CI, 0.72-0.83), which is similar for B-ALL (78%; 95% CI, 0.72-0.84) and T-ALL (80%; 95% CI, 0.70-0.91). These results allow rejection of the null hypothesis of this phase 2 trial that the true median EFS is, at most, 32 months.

In multivariable analysis of presenting clinical features, being older than 20 years and having an initial white blood cell count 30,000/mcl were significantly associated with worse EFS and OS. Presence of minimal residual disease (MRD) at day 28 following initiation of induction therapy and presence of a Ph-like gene expression signature were significantly associated with both worse EFS and OS. Absence of detectable MRD noted in 22 of 58 (38%) evaluable patients at day 28 of induction was associated with 100% EFS (P = .0006). The Ph-like signature was detected in 28% of patients tested on C10403, and the 2-year EFS for these patients was 52% compared with 81% for those without Ph-like disease (P = .04). This large trial, employing an intensive pediatric regimen in AYA patients with ALL, demonstrates a significant improvement (compared with historical controls) in EFS and OS, and validates the approach of using pediat-

ric regimens for treatment of AYAs with ALL by adult hematologists.

A majority of recent studies demonstrate a survival benefit using pediatric regimens for AYA; however, several recently published comparison studies of SAP versus PIP, such as the ABFM,16 found equivalent EFS (□70%). Conceptually, the major difference between PIP and SAP regimens for ALL is in their toxicity profile: whereas PIPs are based on multiple phases and agents (including asparaginase) delivered over the long term, SAP regimens for ALL are focused on aggressive cytoreduction mimicking the approach to acute myelogenous leukemia, including reliance on allogeneic and autologous stem cell transplantation in first CR, fewer consolidations, shorter maintenance durations, and less intrathecal chemotherapy (**TABLE 2**).

THE ROLE OF HEMATOPOIETIC CELL TRANSPLANTATION IN TREATMENT OF AYAS WITH ALL

One of the guiding principles of SAP ALL regimens in AYAs is the idea of proceeding with allogeneic hematopoietic cell transplantation (HCT) as soon as the patient achieves first CR. This is based on a large prospective randomized international collaborative study (MRC UKALL XII/E2993) that documented a significant increase in OS for allogeneic transplant in CR1 compared with a standard ALL regimen (63% vs 52%).[17] On the other hand, the trend in consecutive pediatric studies showed improved outcomes in patients with very high-risk ALL treated with pediatric chemotherapy regimen compared with allogeneic HCT.[18] Similarly, a significant benefit (hazard ratio 3.1; *P* <.0001) in both disease-free survival (DFS) and OS was found in a recent International Bone Marrow Transplant Registry study of adults aged 18 to 50 years for patients receiving an intensive pediatric regimen compared with allogeneic transplant in CR1 due to transplant-related mortality.[19] Thus, one of the major justifications to use an SAP ALL regimen is rendered at least doubtful.

APPROACH TO VERY-HIGH-RISK ALL IN AYAS

Many of the studies reporting on ALL in AYAs have demonstrated that the outcome was closely related to a very-high-risk (VHR) population, including persistent presence of MRD at the end of the induction phase of therapy and the presence of cytogenetic and genomic markers of poor outcome. Presence of genomic markers such as t(9;22)(q34;q11)—the Philadelphia chromosome (Ph+)—results in the expression of the *BCR-ABL1* fusion gene or the *BCR-ABL1*–like (or Ph-like) signature that is characterized by a high frequency of alterations of *IKZF1*, a gene that encodes the lymphoid transcription factor IKAROS and carries a gene expression profile similar to that seen in *BCR-ABL1*+ ALL, but lacks the BCR-ABL1 fusion protein expressed from the t(9;22)(q34.1;q11.2). Both conditions are more commonly found in AYAs; Ph+ occurs in 25% to 30% of older adults, although it is less common in younger adults,[20] and the BCR-ABL–like signature increases with age and is frequent in AYAs (up to 27% in patients aged 20 to 30 years).[20-22]

The current approach to VHR ALL in AYA is to proceed with HCT after induction of remission. Recent data suggest a paradigm shift when it comes to ALL Ph+. Whereas in the past induction therapy following the diagnosis of ALL was followed by HCT, the addition of tyrosine kinase inhibitors (TKIs) to front-line therapy has resulted in prolonged DFS even in patients who did not undergo allogeneic HCT in CR1.[23] The ability of TKIs to achieve major or complete molecular remissions led to the question of whether HCT is needed in all patients. Schultz and colleagues, on behalf of the COG, reported that continuous imatinib exposure improved outcome in a cohort of Ph+ ALL patients with a 3-year EFS of 80% **±11% (95% CI,** 0.64-0.90), more than twice that of historical controls (35%±4%; *P* <.0001).

The 3-year EFS was similar for patients treated with chemotherapy plus imatinib (88% ±11%; 95% CI, 0.66-0.96) and patients who were given sibling-donor HCT (57% ±22%; 95% CI, 0.304-0.761). There were no significant toxicities associated with adding imatinib to intensive chemotherapy.[24] Although this study provides a strong argument that TKI plus standard chemotherapy improved 3-year EFS in children and adolescents with Ph+ ALL, with no appreciable increase in toxicity,[24] further studies are needed to show that TKIs and chemotherapy can replace HCT in AYA with ALL Ph+.

CURRENT STANDARD OF CARE

The current standard of care has been recently reviewed by Curran and Stock.[25] Their recommendations are based on multiple publications that were summarized in a meta-analysis by Ram and colleagues.[14] In this meta-analysis, 11 studies with a total of 2489 patients were reviewed, ranging from 40 to 926 patients per study. The duration of follow-up ranged from 35 to 89 months. None of the studies was a randomized controlled trial.

The analysis showed that AYA patients given pediatric-inspired regimens had a statistically significant reduction in all-cause mortality at the end of the study period (RR 0.59; 95% CI, 0.52-0.66) and at the 3-year mark (RR 0.58; 95% CI, 0.51-0.67) compared with patients given the conventional adult regimens. The absolute risk reduction for all-cause mortality at 3 years was 0.20 and the number needed to treat to prevent 1 death with pediatric-inspired regimens was 5 (95% CI, 4-7). CR rates following induction chemotherapy were superior in the pediatric-inspired regimens arm (RR 1.05; 95% CI 1.01-1.10) at 3 years. Patients in this study arm had higher EFS rates compared with the conventional adult regimes (RR 1.66; 95% CI, 1.39-1.99).

The most important finding was a statistically significant reduction in RR in the pediatric regimens compared with the conventional adult regimes (RR 0.51; 95% CI, 0.39-0.66), without a significant difference in the rate of nonrelapse mortality between the 2 groups (RR 0.53; 95% CI, 0.19-1.48). The balance of the data supports, therefore, that any AYA patient diagnosed with ALL should be considered for a pediatric-inspired protocol, such as the ABFM series of protocols, unless enrolled on a clinical trial investigating the findings reported by several groups,[12,13] indicating no significant differences between AYAs treated on PIP or standard "adult" ones. **EBO**

TABLE 1. Comparison of Outcomes between PIPs and SAPs

REFERENCE	STANDARD ADULT PROTOCOLS				PEDIATRIC-INSPIRED PROTOCOLS			
	n	CR %	EFS %	OS %	n	CR %	EFS %	OS %
Stock et al[5]	124	90[a]	34[b]	46[b]	197	90	63	67
Boissel et al[6]	107	83	38[b]	46[b]	77	94	70	75
Ramanujachar[7]	67	c	49[b]	56[b]	65	c	65	71
De Bont et al[8,d]	73	91, 90[d]	69	38, 45[d]	44	98	34, 34[d]	79
Hayakawa et al[9]	58	94[a]	44[b]	45[b]	78	94	67	73
Rytting[12]	71	99[a]	c	71[a]	85	94	c	74
Usvasalo[13]	97	97[a]	60[a]	70[a]	128[a]	96[a]	67[a]	77[a]

CR indicates complete remission; EFS, event-free survival; OS, overall survival; PIP, pediatric-inspired protocol; SAP, standard adult protocol.
[a]Nonsignificant
[b]*P* <.01
[c]Not reported
[d]1 PIP compared with 2 SAP.

TABLE 2. Comparison of Hyper-CVAD and Augmented BFM

	HYPER CVAD[10]	AUGMENTED BFM[16]
Vincristine	13 x 2/m^2	30 x 2/m^2
Asparaginase	0	47 x 6000 units/m^2
Cyclophosphamide	7200 mg/m^2	4000 mg/m^2
Ara-C	3 g/m2 x16 (total 48 g/m^2)	75 mg/m2 x 32 doses (total 2.4 g/m^2)
Methotrexate	4 g/m^2	2 g/m^2
Dexamethasone	800 mg/m^2	420 mg/m^2
Prednisone	3875 mg/m^2	2280 mg/m^2
IT MTX	12 mg x 8	15 mg x 15
IT Ara-C	100 mg x 8	70 mg x 1
Toxicity profile	Commonly related to myelotoxicty	Frequently related to asparaginase
Duration	Short; proceed with HCT if in CR	Long; 2.5 years in females, up to 3 years in males
HCT	Most of the patients	Limited to very-high-risk patient

Ara-C indicates cytosine arabinoside; BFM, Berlin-Frankfurt-Munster; CR, complete remission; CVAD, cyclophosphamide, vincristine, Adriamycin, dexamethasone; HCT, hematopoietic cell transplantation; IT Ara-C, intrathecal cytosine arabinoside; IT MTX, intrathecal methotrexate.

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PALLIATIVE CARE

The Challenge of Palliative Care for Adolescents and Young Adults

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During the last 20 years, the field of palliative care (PC) has enjoyed a period of scientific growth. Diseases such as Acquired Immunodeficiency Syndrome, combined with new technologies to combat cardiovascular disease, infection, and cancer, have minimized death from acute events and have led to the majority of adult patients dying from chronic, debilitating illnesses.[1] Since approximately 70% of Americans who die each year are elderly, a great majority of palliative care research has been directed toward the care of adults.[2] In pediatric oncology, it is recognized that the needs of children are often overlooked despite the acknowledgment that "children are not just small adults."[3] Despite the expertise gained over the last decade for evidence-based delivery of PC to children, there remains a gap in care for adolescents and young adults (AYA). Strategies utilized for children or adults often miss the complex needs (eg, psychosocial changes, emerging sexuality, and existential loss of future) of the AYA.

ADOLESCENTS AND YOUNG ADULTS AS THE "LOST TRIBE"

AYA have been described as the "lost tribe" in both oncology and in palliative care.[4] This transition period between childhood and adulthood is often defined as 15 to approximately 30 years of age and is marked by tremendous physiologic, developmental, and psychosocial changes.[4] Pediatric PC services are often focused on children under 16 years of age, leading to widening of the gap in care experienced by AYA.[5] This focus on the delivery of PC to children is particularly evident in the American Academy of Pediatrics position statement from 2000, where palliative care for adolescents is mentioned only in the context of requests for euthanasia.[6] The existing PC data for young people between the ages of 15 and 30 years is limited and additional research is therefore necessary to define the specific needs of the AYA population, the goal being to provide optimal service to this population that bridges the transition from childhood to adulthood.

DEVELOPMENTAL STAGES IN AYA ARE VULNERABLE TO CHRONIC OR LIFE-THREATENING ILLNESS

Normal development in the AYA is impacted by life-threatening illness. Widely acknowledged normal adolescent developmental milestones include pubertal development, higher cognitive abilities such as abstract reasoning and risk taking, emerging sense of identity, increasing ability to function independently from parents, and an increasing importance and intimacy in peer relationships. Emerging milestones of adulthood include the establishment of meaningful and enduring relationships; an exploration of identity issues in the worldview, love, and work; a decrease in risky behaviors; and obtaining the appropriate training and education for an occupation.[7,8] For the AYA experiencing chronic and life-threatening illness, these milestones are imperiled. Their growing need for privacy and autonomy is met by invasive procedures, hospitalizations, and increased reliance on parents. When self-esteem and positive body image should normally be increasing, the chronically ill AYA is experiencing amputation, hair loss, and weight loss or gain. Most importantly, in the period of time the AYA would normally develop independence, peer relations, and sexual identity, chronic illness limits—or completely prevents—achieving these important milestones. The conflicts of development caused by chronic or life-threatening illness can lead to acting out, high-risk behaviors, and even poor compliance with treatment.

DOMAINS OF PALLIATIVE CARE IN ADULTS VERSUS AYA

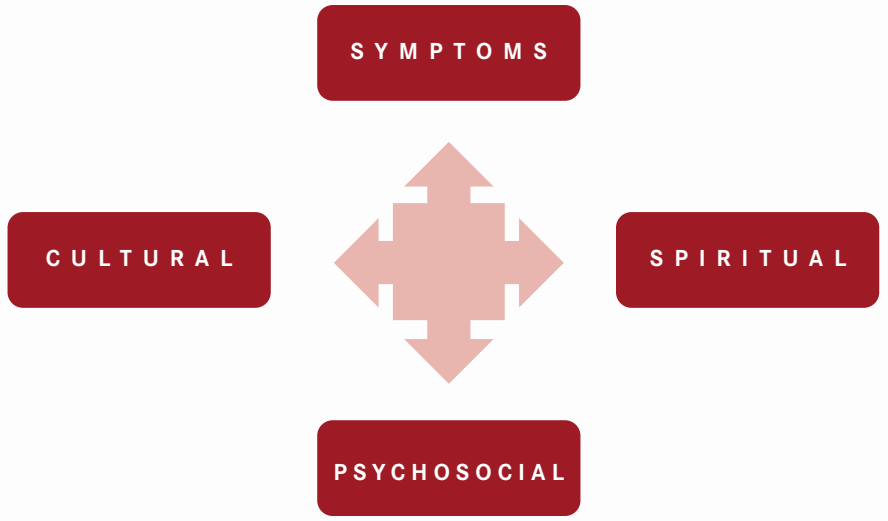
In the last 2 decades, PC for adults has experienced significant growth and 4 specific, interdependent domains of care have been commonly identified (**FIGURE 1**). In the AYA, the domains of PC become more complex (**FIGURE 2**) with the realms of developmental and legal issues added, and a stronger role of communication between the multidisciplinary healthcare team and the AYA becomes imperative. Even though AYA <18 years of age are considered "minor," most experts conclude that children >14 years (or even younger if experiencing prolonged chronic illness) have the functional capacity to make medical decisions.[9] In particular, the domain of spirituality is enlarged secondary to existential issues (loss of future, loss of sexual or relationship milestones) commonly observed in the AYA population.

Symptom control in the AYA has the most PC data in published literature. In oncology, symptoms experienced by the AYA are quite often linked with the location of the cancer (eg, bone tumor vs leukemia vs brain tumor) with frequency of symptoms in adolescents with cancer being as follows: fatigue (86%), reduced mobility (76%), pain (73%), poor appetite (71%), and shortness of breath (21%), with 50% of patients suffering 3 or more symptoms.[10] Although symptoms at the end of life are treated as for any child

or adult, the interaction of the physical suffering with the psychological, developmental, spiritual, or cultural influences common to the AYA demographic may uniquely impact and worsen the degree of total suffering experienced by the AYA.[11] This concept of AYA-specific stressors leading to worsened symptom control must be an important consideration in all AYAs treated for cancer, especially at the end of life.

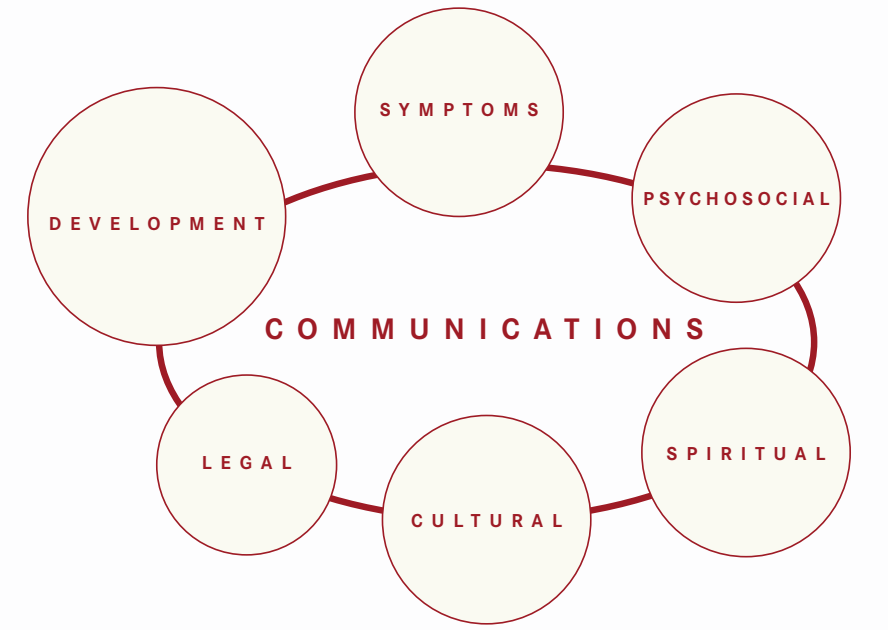
The psychology of dying is also influenced by AYA-specific stressors. The dying AYA faces the challenges of not being able to socially mature (overly protective parents, learned passivity), social rejection by peers (which undermines self-esteem), social isolation, and lack of sexual outlets.[9] The end result can be high-risk behavior (HRB), regression, poor compliance, anxiety, and depression. HRB includes high-risk sexual experimentation, violence, illicit drug use, and potentially self-harming activities (eg, snowboarding when orthopedically contraindicated). Protective factors (high intelligence, cohesive family, good role models, and religious beliefs) that reduce the chance of HRB often relate to stable social factors and premorbid development of healthy coping skills.[12] Lastly, sexual behavior and risk taking is often overlooked by health professionals in the chronically or terminally ill AYA patient—up to 26% of chronically ill patients ages 14 to 18 years, and up to 43% of visibly ill patients (eg, suffering from cerebral palsy or multiple dystrophy) are known to be sexually active.[12,13] A majority of AYA who are sexually active report no formal discussion about contraception or safe sex practice. In addition, the sexually transmitted disease (STD) rate has been documented as being higher in the visibly ill AYA patient and is possibly related to the chronically ill being more susceptible to infection.[13] The desire for normalcy, intimacy, and acceptance likely puts the chronically or terminally ill AYA at risk for STDs, and therefore communication about sexual practice and increased screening for sexually transmitted infections needs to be included as part of the global assessment for this population, particularly in the early phases of their disease trajectory.

FIGURE 1. Domains of General Palliative Care



The 4 domains interact with and are codependent on each other.

FIGURE 2. Domains Of Adolescent And Young Adult Palliative Care (AYA PC)



Unlike general palliative care, the domains seen in AYA PC include both development and legal issues. Although interaction and codependence of the multiple domains still exist, the most important aspect of AYA PC is multidisciplinary communication which binds all domains together for total care of the AYA.

SPIRITUALITY IN AYA PALLIATIVE CARE

Spiritual crisis or existential loss is a major theme that AYA face during a life-limiting disease. Spirituality integrates mind, body, and spirit into a sense of wholeness and well- being.[14] In the context of AYA palliative care, the extent of the loss of self and future dreams and goals (eg, marriage, career, family, interacting with peers, or loss of limb through amputation) is not known. Although most healthcare professionals believe in the importance of spiritual assessment,[14,15] few address spiritual needs beyond religious beliefs and practice.

Sexuality must be considered a component of spirituality in the AYA patient. In the early phases of the illness trajectory, it may be difficult for parents and the healthcare team to consider the AYA as a sexual being, leading to embarrassment (eg, masturbation during hospitalization), guilt (eg, yet undisclosed sexual orientation or gender issues), or even morbidity (eg, unprotected sex with high-risk partners). When acting out or noncompliance is seen in the AYA patient, it might be a sign of existential (spiritual) crisis that warrants further discussion and acknowledgment to ultimately address the overall domain of spirituality in the AYA patient. During later phases of the terminal illness, sexual issues may be overshadowed by physical suffering (eg, pain), but communication should remain open particularly to diffuse negative influences on the AYA patient's spirituality (eg, guilt, sense of being punished, or imposition of parental beliefs).

MULTIDISCIPLINARY MODEL TO DELIVER AYA PALLIATIVE CARE

The dying AYA represents a developmentally unique patient group that requires a fully functional multidisciplinary team to assess and deliver high-quality end-of-life care. Communication between the AYA and the healthcare team may be challenged by barriers inherent to AYA psychology. Ultimately, appropriate education of healthcare staff with an emphasis on communication, compassionate delivery of emotional or psychological symptom relief, and development of skill sets to address spiritual suffering is needed to deliver optimal palliative care to these AYA patients. **EBO**

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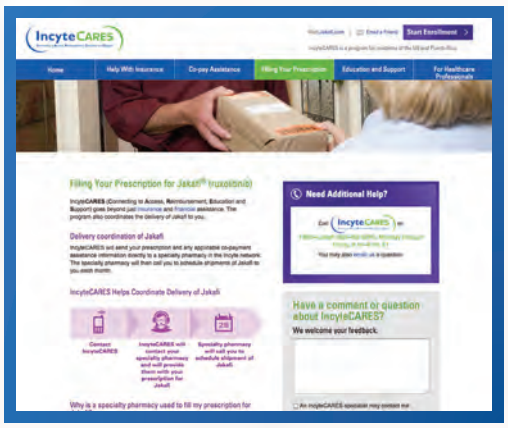

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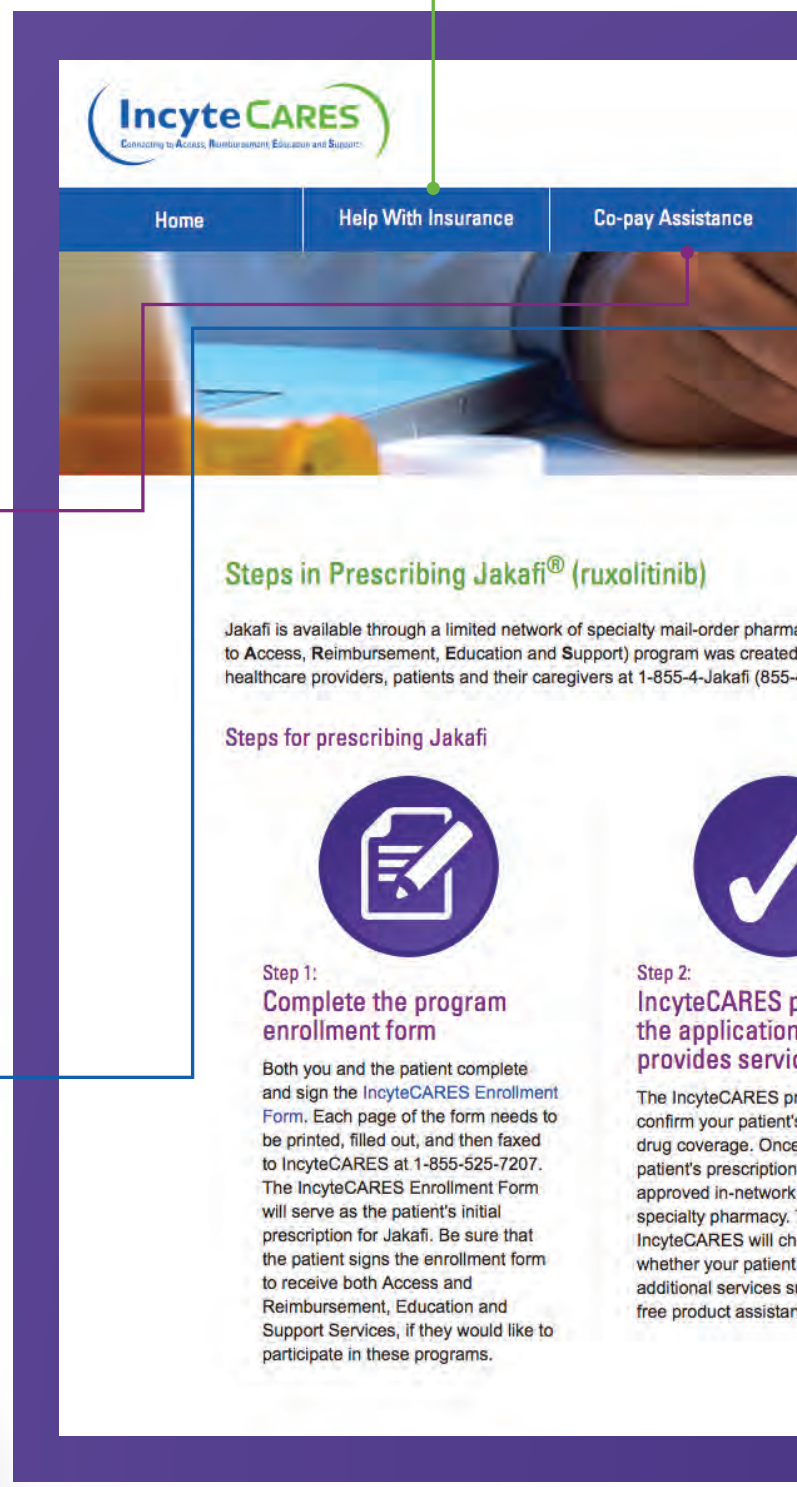

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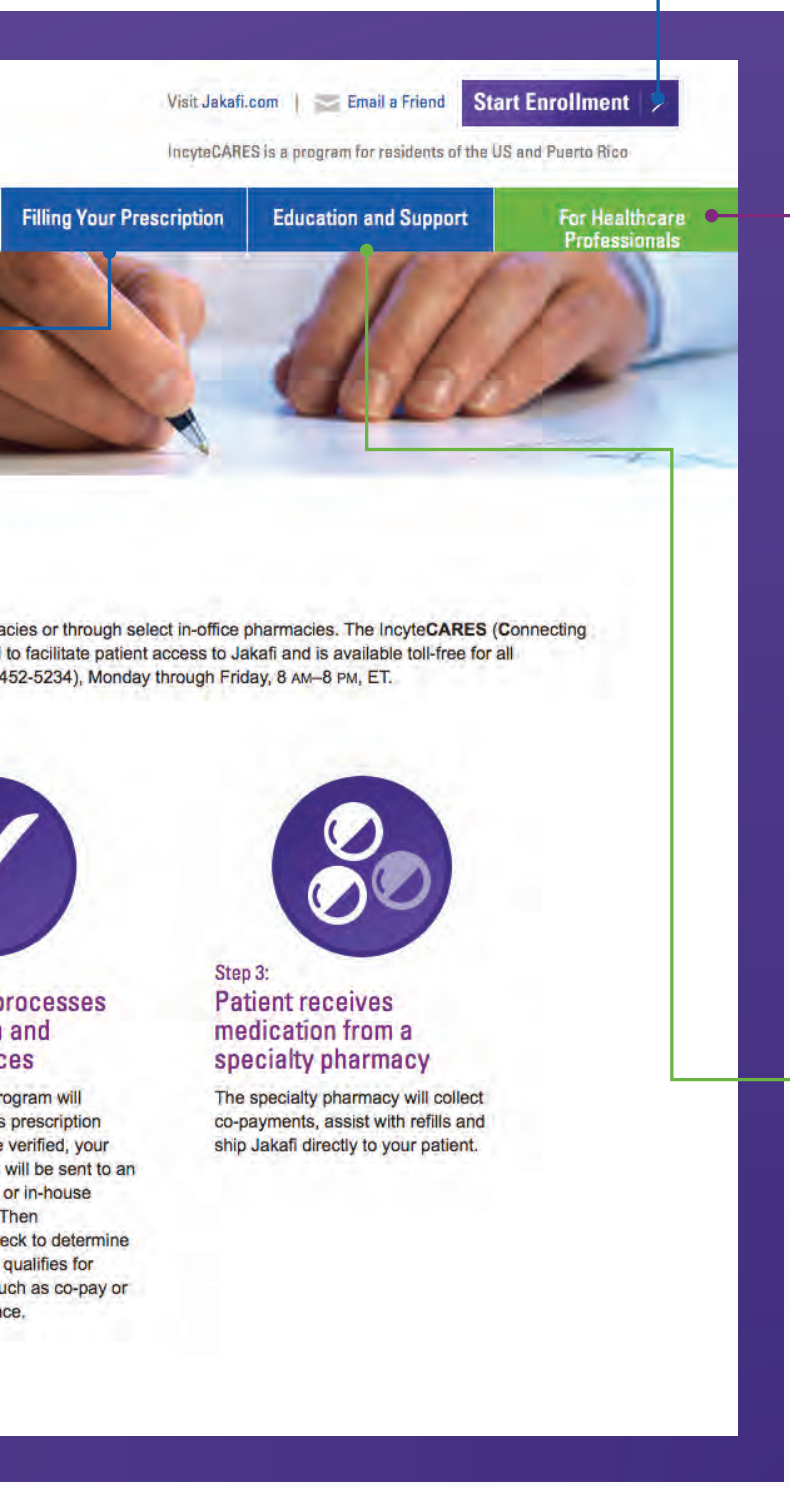

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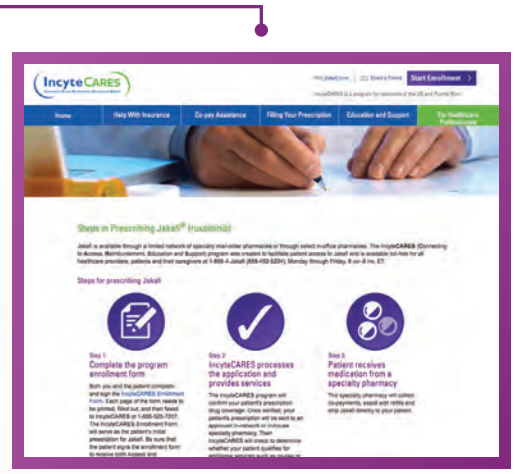

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Dr Mody is a pediatric oncologist at the University of Michigan Health System.

C.S. MOTT CHILDREN'S HOSPITAL
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Rajen Mody, MBBS, is a pediatric oncologist at the University of Michigan Health System. Dr Mody, who has been a part of several drug development trials for pediatric cancer conducted by the Children's Oncology Group, is currently investigating the application of precision medicine through the use of next generation sequencing (NGS). He recently co-authored a paper in *JAMA*,[1] evaluating the use of integrative clinical sequencing and genetic counseling when treating pediatric and young adult (YA) patients with cancer.

Evidence-Based Oncology spoke with Dr Mody about his experiences when treating this patient population, the survivorship program offered by the University of Michigan to help with care transition, and his belief in NGS as the path to improved patient outcomes.

What are some of the challenges faced by healthcare providers when treating pediatric and YA patients who have cancer?

Our biggest challenge is the small numbers of these patients—there are only about 13,000 to 14,000 new cancer diagnoses in North America, which, in a way, is a good problem to have. But with respect to clinical trials and advancing cancer care, there is need for a certain number of patients; fewer patients, especially with hard-to-treat cancers, can be an impediment in terms of pharmaceutical interest [in developing specific drugs].

Also, among young patients being treated for cancer, the associated toxicity is heart-wrenching. Pediatric and YA patients are quite resilient to harsh medical treatment, considering that most pediatric chemotherapy regimens that we use are much greater in intensity than the adult regimens because most pediatric cancers are very aggressive. Younger patients actually tolerate the regimens really well and that has led to nearly 75% to 80% of patients in long-term remission, nearly 70% of whom are cured.

We have, however, become a victim of our own success, with the myth that pediatric cancers are very treatable. The problem is the 30% of patients who end up with a recurrence; the curves have not shifted for those patients in the last 15 years…the improvements have plateaued. The absolute number of 70% needs to improve, and that's where some of the research that our group is involved in—where we are sequencing every tumor that has relapsed or has metastatic disease—will help.

The hard-to-treat population—that is, patients who have relapsed following frontline treatment—are the ones we included in our recently published study[1] for which we conducted whole-exome sequencing on patient tumor samples and gathered information that helped modify treatment regimens in nearly 50% of the patients analyzed. Even with the 70% of patients who are cured, we would like to sequence their tumors and gain information that would allow for less toxic treatment, avoid radiation treatment, or even change diagnosis in some cases.

How long are survivors followed? Do you work with the child's pediatrician post diagnosis and during cancer treatment?

Most programs, including ours at the University of Michigan Health System, follow the patient until they are 21 years of age or 10 years from diagnosis, whichever is later; some programs follow these patients until they are 25 years of age. There are a few YA survivor groups that follow them for an even longer duration.

The biggest challenge is the transition of care, and the biggest resistance we face is sometimes from parents. However, we, as pediatric oncologists, want to mainstream the patient and so we do try to explain to the parents the important role played by the child's pediatrician or primary care physician in care continuum.

Rajen Mody, MBBS, with a patient. Photo courtesy of the University of Michigan Health System.

Our strategy is to co-manage the patient a few years prior to transition. The patients continue to see their pediatrician while they are in our care, but about 2-years before transition, we help them transition out of our care. Our team also assists with identifying a good physician and establishing care if the patient will be transitioning to a new geographic location. We also share the Passport for Care[2] with the survivor and the future provider. And while we do attempt to work with the transition, many times we are not able to identify good pediatric and family practice doctors comfortable with complex patients like these.

[At the University of Michigan,] we have a long-term survivorship program that is staffed by physicians, nurse practitioners, social workers, a school teacher within the hospital, a dietician, and several administrative staff members who help with the entire process. It is clearly a team effort.

How important is integrating psychosocial aspects into the care plan?

We have a combined team of pediatric and adult oncologists that takes care of the YA population at our hospital, based on whether they have an adult or pediatric type of disease. In addition to the physicians, we have special clinics that cater to the educational needs of the YA patients and offer early or really late appointments or weekend infusions etc.

We have a resident school teacher who helps the YAs with homework and even "teaches the teachers" to work with YAs who are undergoing chemotherapy infusions but are planning to take their SATs. Social workers on our team maintain special hours to accommodate this population of patients. Additionally, infusion rooms have separate pods for teenagers so they can get the privacy that they might crave, and nurses and teams familiar with YA care are specifically assigned for care management.

Does your cancer center offer fertility services?

Parents are quite aware and maybe more involved than the YA when it comes to fertility preservation. The teenagers themselves are sometimes not interested in discussing options, either due to embarrassment or the contradiction of speaking about their disease and then fertility in the same breath. Parents, however, want us to discuss the options with their teenager, maybe because they had never broached this topic at home prior to their child's diagnosis.

Although most parents do want the option, sometimes it may not be practical, especially if treatment needs to be initiated immediately [depending on the diagnosis], because there are some technical challenges associated with this, particularly for girls. The process is much more involved for girls because they need to be medicated to induce ovulation to collect oocytes and there could even be a minor surgery involved. This can sometimes lead to care providers not opting to offer the option to patients. Sometimes, the aggressive nature of their disease may not leave the

option of waiting to start treatment.

I do hope that the situation improves for YA girls receiving cancer care. In our survivorship clinic that I was a part of and ran for about 5 years before I moved into more translational genomic research, we learned that our inability to help YAs with fertility preservation actually has a much greater impact on women's survivorship.

In your experience, does insurance access influence care decisions made by family members?

With our precision oncology approach in pediatric oncology, we have had a slightly easier time in getting off-label drugs than our colleagues who treat adult cancer patients. Most of the drugs used in pediatric oncology are off-label because [the pharmaceutical industry] will not develop drugs for a small patient population. We have been quite successful in gaining access to drugs based on the results of our genomic analyses, and we appreciate the cooperation we have received from payers to consider our request for treatment of our pediatric cancer patients, guided by precision oncology.

I expect there will be an increasing trend where patients will approach third-party payers with genomic evidence of a particular molecular aberration. The treatment would obviously need to be carried out under the umbrella of a clinical trial, but the fact remains that there just aren't enough clinical trials being conducted for pediatric oncology patients.

There are great expectations from the NCI-MATCH trial. Do you think pediatric and YA patients could also benefit from a similar trial design?

I am actually a part of the pediatric version of the NCI-MATCH trial, which we are hoping to initiate sometime next year. We are currently finalizing the agents to include, and we will then set up discussions with the pharmaceutical industry to see whether they'd be willing to provide the necessary agents for the trial.

NGS of course can provide a tremendous amount of data. What are the advantages and some of the challenges of clinical implementation of this technology?

Genomic sequencing clearly identifies actionable mutations in only 50% of the population. Our recent results tell us that we need to temper down our enthusiasm around this technique, especially for parents who are always expecting an answer. While NGS provides us answers for 50% of patients, only 25% of those could actually be acted upon owing to logistical challenges. These challenges include the drug not being accessible, the available drug might be the wrong dose or formulation, long turnaround time for NGS results, and cost of the analysis.

I do think, however, that NGS analysis will soon be much cheaper and the turnaround time will reduce; however, the technology itself needs to evolve and the NGS panels should be developed to analyze epigenetic findings so they can truly impact patient care. The central message remains that we need more drugs developed specifically for pediatric cancer patients.

While we have made great strides over the last 4 decades in terms of care rendered and outcomes of pediatric cancer patients, a lot more efforts are necessary for the 25% to 30% of hard-to-treat patients who do not benefit from the current standard-of-care treatments. I believe precision oncology and immunotherapy will hopefully lead the way to provide improved outcomes for the hard-to-treat patients. Ultimately, though, care for young cancer patients does not culminate with their cancer treatment; efficient survivorship programs are as important for them to lead a healthy and meaningful life. **EBO**

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LITERATURE REVIEW

Using a Gene Expression Assay to Predict Response to NAC in Breast Cancer

SURABHI DANGI-GARIMELLA, PHD

Described by the National Cancer Institute as treatment administered prior to the primary therapy,[1] neoadjuvant chemotherapy (NAC) for women diagnosed with breast cancer can help shrink a tumor prior to surgery, which can make the procedure minimally invasive and potentially influence prognosis.

Research has shown that chemotherapy prior to surgery can allow for a lumpectomy instead of a mastectomy, resulting in breast conservation. One such study published in the late 1990s monitored 1523 women enrolled in the National Surgical Adjuvant Breast and Bowel Project B-18. Clinical tumor response (complete, partial, or none), disease-free survival, distant disease-free survival, and survival were monitored and compared between randomly assigned preoperative and postoperative chemotherapy groups. The results showed that although preoperative chemotherapy is as effective as postoperative chemotherapy, treatment prior to surgery allows significantly more lumpectomies and is suitable for patients with early stage disease.[2]

Tests that can predict patient response to NAC can help determine eligibility for chemotherapy and protect patients from unnecessary exposure to poisonous treatment if it will not be effective. A study published in the journal *Clinical Cancer Research* has done just that.[3] In collaboration with the developers (NanoString Technologies) of the Prosigna assay, the authors evaluated the performance of core needle biopsy (CNB) samples and determined if the Prosigna risk of relapse (ROR) score and intrinsic subtype could identify patients who will not respond to NAC, thus preventing unnecessary treatments and the associated cost.

The Prosigna assay uses gene expression data which is weighted with clinical variables to generate an ROR score to predict risk of distant recurrence. The authors evaluated the combination of Prosigna ROR and intrinsic subtype as predictor of response to multiagent NAC in HR+/HER2 patients. They also examined whether the ROR score of a CNB sample and the corresponding surgical resection specimens (SRS) were correlated.

STUDY SAMPLES

The authors collected 122 formalin-fixed paraffin embedded (FFPE) tumor blocks with CNB samples from 95 patients who were newly diagnosed with breast cancer between 2008 and 2014 (designated as the CNB sample set). The metastatic study population included 40 FFPE tumor blocks containing CNB or excisional biopsy samples from metastatic lesions in the skin, lymph node, lung, and liver, gathered from a single institute. The SRS study population included 30 independent samples selected from the CNB development sample set that had a corresponding CNB. Surgical resection was between 14 to 21 days following biopsy. Chemo-prediction validation was conducted in 216 HR+/HER2-breast tumor samples from a multi-center Spanish cohort. Outcomes in 180 CNB samples from HR+/HER2 patients treated with NAC, measured as pathological response, was correlated with ROR.

ANALYSIS AND RESULTS

Intra- and inter-biopsy variability, the authors found, was 2.2 and 6.8 ROR units, respectively, as evaluated from 79 CNBs from 30 independent tumors. A high correlation in ROR score was observed between 33 paired CNBs and SRS ($R \geq 0.9$). Individual gene correlation between CNB and SRS, conducted for each gene included in the Prosigna assay, identified a median correlation coefficient of 0.91.

When evaluating the molecular subtypes of biopsied breast tissue samples, the Prosigna test could successfully classify 85.7% of ER-negative samples as nonluminal, 90.6% of ER-positive samples as luminal, and 100% of HER2-positive samples as HER2-enriched. Univariate analysis of ROR score, intrinsic subtype, and residual cancer burden (RCB, which determines the overall NAC response rate) found that the continuous ROR score was a significant predictor of response to NAC. The authors also found that the ROR score is greater for tumor samples that have an increased expression of genes that drive cell proliferation. More specifically, a 20-point increase in the ROR score increased the likelihood of a patient's response to NAC by 59.1%. Prosigna ROR score and intrinsic subtype are strong predictors of response to chemotherapy in the neoadjuvant setting, the authors conclude. **EBO**

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Picking Up the Pieces—Thoughts on Cancer by a 25-Year-Old 8-Time Cancer Survivor

WOODROW ROSELAND

ABOUT THE AUTHOR

WOODROW ROSELAND

Mr Roseland is a 25-year-old 8-time cancer survivor. On any given day you can find him with his head in the clouds at Cheeseman Park in Denver, Colorado. He enjoys photography and bike rides. Woody pays his rent by producing short films for companies and nonprofits.

Woody is an active member and advocate for the adolescent and young adult cancer community, working to raise funds for fellow cancer patients and survivors. A couple of nonprofits Woody believes in are Pelotonia and First Descents, and he thinks it would be cool if you gave them a couple dollars.

Cancer is kind of like childhood. When you're in the midst of it, you assume that everyone has it exactly the same as you—whether that's weekends at the lake or afternoons with Cytoxan. But eventually, if you're lucky, you make it out in 1 piece and attempt to live a "normal" life. Over time, you even accrue little nuggets of wisdom and information here and there that make you realize this experience is much bigger than you could have ever imagined. Although everyone went in with good intentions, mistakes were made, things slipped through the cracks, and now you're left as the owner of the consequences of those decisions, good *or* bad.

I'm 25 years old right now. Thinking back to when and how I was diagnosed at 16 years old is difficult. For all intents and purposes, I found out that I had cancer as a child. I relied on my parents for everything. I relapsed 7 times over the next 7 years, effectively growing up with my cancer, taking time off from high school and college to get treatment. I watched friends graduate and accept internships while I smoked weed and watched SportsCenter on my dad's couch.

My role as a patient was simple—accept the suffering I had to endure. There was no way out except through a gratuitous amount of suffering. And that's fine; that's the way it is. But it becomes hard to find the line between when to suffer and when to question. When do you put your foot down and demand a second opinion, more pain medications, less treatment, or more treatment?

Some things about my experience were really hard. I lost my left leg to an amputation. I was given a drug that wrecks male fertility, and nobody told me. It wasn't until I relapsed years later and had to take the same drug again that I was told that my fertility was ruined.

The realist in me knows that suffering is part of the human experience and that I'm in no way unique in my suffering. But I don't think that should give doctors, nurses, and other healthcare providers a free pass on the nuanced aspects of adolescent and young adult healthcare.

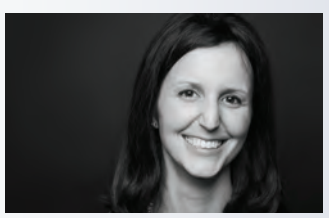
As I learn more about myself as a person, I see that I'm bad at asking for help, that I'm good at enduring pain, and that I hate to inconvenience others. Which might not be the best combination for a cancer patient. Sitting in an exam room with my oncologist, the options seem very black and white—what she recommends and what she doesn't—but that negates an entire world of other opinions that could save my life.

If I could give my 16-year-old self any advice when I was diagnosed, I would probably tell him that it's going to suck a lot. Your cells are going rogue and the fact that they are turning on you in no way reflects on you as a person. There are a lot of people out there who want to help you, and it won't hurt that much for you to let them. It's worth putting in the extra effort to get it right instead of jumping into something quickly because you feel that's what you're supposed to do. Also, girls named Heather are trouble and should be avoided. **EBO**

Financial Toxicity and the Young Adult Cancer Survivor

SAMANTHA WATSON, MBA; AND MICHELLE S. LANDWEHR, MPH

ABOUT THE AUTHORS



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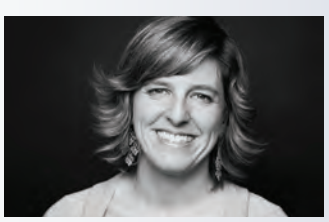

MICHELLE S. LANDWEHR, MPH

Ms Landwehr is COO, The Samfund.

There are currently 630,000 young adults (YAs) in the United States with a history of cancer.[1] Due to the overwhelming costs of cancer, many find themselves struggling financially post treatment—facing ruined credit, depleted savings, looming homelessness, and other dire circumstances.

Although "financial toxicity"[2] is finally being recognized as a legitimate and common after-effect of cancer treatment (thanks to 2014's *60 Minutes* piece on the cost of cancer drugs and the team of doctors who recently published their case for lower costs[3]), we at The Samfund for Young Adult Survivors of Cancer have seen for over a decade how cancer can derail the financial health of YAs. In many ways, it is their life stage—more so than their specific diagnosis or treatment—that complicates their financial recovery: their schooling has been interrupted, their careers are stalled, and moving forward feels impossible. Compounding their struggles is the dearth of age-specific financial support services.

the samfund
support for young adult cancer survivors

The Samfund is proud to be the first and largest organization in the United States uniquely designed to help YAs recover from the financial impact of cancer. It was founded in 2003 by a 2-time YA cancer survivor to provide financial assistance to YAs post treatment, regardless of diagnosis or where they live. Since 2005, The Samfund has distributed close to $1.5 million in grants and provided free online support and education through its website to YA survivors across the country facing great financial need due to cancer.

Many YAs lack the employment history of older adults, lack the family support of younger children, and are caught between being too old to be covered by their parents' insurance and too young to comfortably afford their own. As a result, many YAs face impossible decisions about which bills to pay and which to forego, whether to bankrupt themselves to pay for health insurance or risk going without, and how to keep moving forward when there are so many obstacles in their way. Finishing treatment and having the freedom to move forward with their lives should be a relief, but the sudden reality of medical bills, coupled with drained savings accounts and limited employment options, is often more daunting than celebratory.

As one Samfund grant recipient wrote, "[My last date of treatment] should have been a day to celebrate, but instead it was a day when the reality sank in. Yes,

I was cancer-free, but I was also broke. From that point forward, every bill has been a struggle to face. There's just nothing left after I've paid my normal personal bills of rent, car payments, grocery bills, school loans, and so on. So, the bills have accumulated. The hospital calls regularly to urge me to pay more. I always pay what I can, but that leaves me with nothing to help rebuild my savings account, to visit friends, to buy a pair of shoes, or get ahead."

FINANCIAL BURDENS ARE COMMONPLACE

Unfortunately, this sentiment is not uncommon. A study by Duke University and Dana-Farber Cancer Institute researchers found that even with insurance, cancer patients pay an average of $712 out-of-pocket for treatment-related expenses per month—an average of $8544 a year.[4] For patients without insurance, the cost is exponentially higher, and the expenses continue even after treatment ends. Follow-up care for those declared cancer-free can exceed $4000 a year. Not surprisingly, this financial toxicity can lead to poor health outcomes for YAs. We have sought to improve these outcomes through our programs.

Another Samfund grant recipient wrote, "I'm always told to focus on 'me' and 'getting better,' but that is almost impossible with all of the stress of post-treatment side effects, depression, and financial burden that cancer and treatment has created in my life."

There are additional "collateral costs" related to financial toxicity. According to the results of a survey conducted by the Association of Oncology Social Workers, 66% of cancer patients with major financial challenges suffer from depression or anxiety.[5] Sixty-three percent of oncology social workers surveyed in that same study reported that financial issues reduce patients' compliance with their cancer treatment even though that treatment is key to their recovery. Additionally, 40% of patients reported depleting their savings, almost 30% reported dealing with bill collectors, and 54% of those handling a major financial burden said it had become more difficult in the past year to afford treatment. These results were echoed in a needs assessment conducted by The Samfund, which showed that 46% of respondents were "very uncomfortable" with their financial situation and 74% struggled with reducing debt and paying monthly bills.

PROVISIONS WITHIN THE AFFORDABLE CARE ACT ARE A BIG HELP

We were greatly encouraged by the outcome of the *King v Burwell* case upholding the Affordable Care Act (ACA), especially because of the potential impact on the YA population. Anecdotally, we know that many YAs have gone without health insurance (pre- and post treatment) because of the cost and/or are skipping follow-up appointments because they have too many medical bills. Many say they are often embarrassed to see their doctors because they are behind on their payments.

Two of the mandates of the ACA will directly impact the ability of YA cancer survivors to get coverage: (1) they can remain on their parents' insurance plan until age 26 years, and (2) providers can no longer deny coverage due to a preexisting condition. We have heard stories from YAs who found themselves uninsured at the time of diagnosis becoming saddled with hundreds of thousands of dollars in medical debt by the time their treatment is complete; obtaining an insurance policy with this preexisting condition was an impossibility. This policy change is completely life-altering for those who have found themselves in a similar situation after the ACA went into effect.

Jonathan S, a 31-year-old survivor of testicular cancer, told us, "With a few months left on my COBRA health insurance, I was paying nearly $650 per month for my premium. As my coverage was coming to an end, I knew no insurance company would insure me if [it] weren't for the ACA. Because of the ACA, I have been able to purchase an affordable plan that suits all my needs."

In spite of these positive developments, much confusion remains regarding how exchanges work, what subsidies exist, and if YAs can get quality medical care as cancer survivors. One of our goals as an organization is to educate this group about their options and their rights in terms of healthcare. To that end, we are proud to partner with Triage Cancer on a new program, Finances 101: A Toolkit for Young Adults with Cancer. This program will educate YAs with a cancer history on financial decision making at key junctures during their treatment and recovery in an effort to abate or prevent the financial toxicity so common in this age group.

We hear from many YAs who are now covered or whose premiums are now far less expensive as a result of the ACA, so we are seeing some improvement already. However, there are many who are still dealing with high deductibles and premiums that are more than they can comfortably afford or who are still without coverage. There is a lot more work to be done. An increase in marketplace options, ongoing education regarding the various available insurance options, and communication with healthcare providers on treatment costs will all contribute to improvement in health and psychosocial outcomes in this population. **EBO**

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340B: REBUTTAL

Sticking Up for the 340B Program

ROBERT CHAPMAN, MD

The federal 340B drug discount program helps hundreds of thousands of needy Americans receive life-saving cancer treatments each year. Unfortunately, there is a lot of misinformation circulating about the growth and purpose of the program, misinformation that is creating an atmosphere of undeserved mistrust and criticism of hospitals that use 340B discounts to help treat the needy.

Here are some facts:

- There has been a cascade of hospital acquisitions of private practices across all disciplines for several reasons, including reduced reimbursements under the Medicare Modernization Act of 2003. Critics tar the 340B program as a culprit when there are no credible data showing safety-net hospitals buy private oncology practices any faster than non-340B hospitals. Physicians remain free agents as this trend proceeds, and they cite increased administrative burdens and costs for information technology as key drivers in their decisions to work for hospitals. Medicare drug costs in private practice remain considerably higher at $9.7 billion per year compared with $6.0 billion in the hospital setting.[1]
- Hospitals are not manipulating the program when they acquire medications for insured patients at 340B prices and bill at negotiated rates. Congress designed the program this way to enable providers to make a margin and stretch scarce resources to cover the needs of the patients they serve.[2] The program helps safety-net hospitals fund clinical services as well as free and discounted drugs for underserved and uninsured patients who cannot afford to pay for oncology care. Discounted and free drugs reduce readmissions and help ensure that patients follow physician-ordered clinical regimens.
- Oncologists in a safety-net hospital provide high-quality, protocol-driven care in which the patient is the first priority. Medicare pays 340B hospitals more for oncology and other services in recognition of the continuous need for safety-net services. Private oncology physicians are not obligated to provide care to poor patients and often cannot afford to do so. Many are grateful for the services hospital clinics offer to patients who cannot pay or are underinsured. In addition, accredited hospitals must meet many other standards and requirements that add costs, which private offices do not face. Hospitals also offer a much broader range of oncology services, including advanced diagnostics, surgery, radia-

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FIGURE. Facts on 340B Disproportionate Share Hospitals[3]

tion therapy, infusion services, patient and family counseling, home care services, and palliative care.

- To qualify for reduced 340B drug pricing, hospitals have to certify annually that they serve a disproportionately high percentage of Medicaid and low-income Medicare patients. Overall margins at many 340B hospitals are slim to none, despite savings from 340B discounts. 340B assures that pharmaceutical companies contribute to the costs of assuring care for the poor. 340B hospitals deliver about twice as much care to Medicaid and low-income Medicare patients as other hospitals. These safety-net hospitals also provide much more uncompensated care—nearly $25 billion per year (see **FIGURE**).[3]

The Henry Ford Health System is grateful to be able to provide care in a national system that allows our hospitals and our doctors to be blind to a patient's economic circumstances. In 2014, we provided more than $314 million in uncompensated care. Because of 340B and other safety net programs, we are able to continue our founder's mission to serve everyone, regardless of their ability to pay. Detroit has no public hospitals and only a handful of federally qualified health centers. Thanks in part to 340B savings, we are able to fund 4 oncology clinics and keep them open for all patients in Detroit and surrounding townships.

Changes in the healthcare marketplace are steadily pushing changes for physicians and specialty practices of all kinds. Blaming the 340B drug discount program is both misleading and unproductive. Broad-based payment reform in oncology is desperately needed, regardless of the site where that care is offered. **EBO**

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ASCO: Advanced Lung Cancer

SURABHI DANGI-GARIMELLA, PHD

The American Society of Clinical Oncology (ASCO) released an update to its clinical practice guideline for stage IV non-small cell lung cancer (NSCLC). Published in the *Journal of Clinical Oncology*[1] the guidance provides recommendations for using systemic therapy—chemotherapy as well as targeted therapy—in first-, second-, and third-line regimens. Following a systematic review of published literature that includes data from 73 phase 3 randomized clinical trials over a 7-year period between January 2007 and February 2014, a panel of experts from ASCO developed the following key recommendations:

FIRST-LINE TREATMENT

- If tumor lacks *EGFR* or *ALK* gene alterations, combination cytotoxic chemotherapy for patients with performance status 0-1 is recommended. For patients with

performance status 2, chemotherapy or palliative care alone may be used.
- If tumor has sensitizing *EGFR* mutations, afatinib, erlotinib, or gefitinib is recommended.
- If tumor has *ALK* or *ROS1* gene rearrangements, crizotinib is recommended.
- First-line cytotoxic chemotherapy should be halted if disease progresses or if patients are nonresponsive following 4 cycles.

MAINTENANCE THERAPY (TREATMENT AFTER INITIAL RESPONSE TO FIRST-LINE TREATMENT)

- Patients may be recommended to either switch to another regimen, or continue first-line therapy, or take a break from chemotherapy.

SECOND-LINE TREATMENT

- Docetaxel, erlotinib, or gefinitib are options; pemetrexed is an additional option for patients with nonsquamous cell carcinoma.
- Docetaxel, erlotinib, or gefinitib can be used for squamous cell carcinoma.
- Patients with *EGFR* mutations can receive combination cytotoxic chemotherapy or another *EGFR* inhibitor, depending on initial response.
- Patients with *ALK* rearrangements who have progressed following crizotinib treatment may be offered chemotherapy or ceritinib.

THIRD-LINE TREATMENT

- Erlotinib may be offered for patients

with performance status 0-3 who have not previously received erlotinib or gefitinib.
- Insufficient evidence to recommend routine third-line cytotoxic drugs.

Emphasizing that age alone should not be a factor in the selection of treatment, the guideline recommends early palliative care, along with antitumor treatment. The key takeaways of this update are that there is no cure for patients with stage IV NSCLC and that age should not be the only determinant of key decisions on chemotherapy treatment.

"Although there is no cure for patients with stage IV non-small cell lung cancer, various treatment options are available that can help patients control their cancer longer," said Gregory Masters, MD, who co-chaired the panel, in a press release.[2] "This guideline will help doctors choose the most appropriate therapies, depending on the biology of the tumor and the patient's general well-being."

Co-chair David H. Johnson, MD, emphasized the importance of palliative care in this patient population. "Early palliative care is associated with improved survival of patients with advanced lung cancer," he said. "Hospice care also improves patient quality of life and reduces caregiver distress." **EBO**

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ASCO: Genomic Testing for Cancer Susceptibility

SURABHI DANGI-GARIMELLA, PHD

While the technology driving the development of newer genetic tests and multigene panels has gained rapid strides, providers struggle with knowledge gaps and assurance of test validity. Recognizing these and other issues is a policy statement that was released by the American Society of Clinical Oncology (ASCO); the updated recommendations by ASCO were published in the *Journal of Clinical Oncology*.[1]

Albeit the significant advantage that genetic testing panels bring to oncology care, the field remains a work-in-progress. Providers and payers continue to question[2] the clinical validity and utility of diagnostic tests. Oncologists constantly struggle when determining the "value" of gene tests considering the high costs associated with some of the panels.[3]

With the new recommendations, ASCO wants to ensure optimal deployment of current and future innovative gene technologies in clinical practice. ASCO president Julie M Vose, MD, MBA, FASCO, said in a statement,[4] "As cancer diagnosis and treatment is becoming more genetically-driven, new opportunities and questions are emerging about screening for hereditary cancers. ASCO is releasing this updated policy statement at this critical juncture to ensure that all interested parties thoughtfully consider these concerns as the future of genetic and genomic testing for cancer susceptibility unfolds."

ASCO's Cancer Prevention and Ethics Committees have 5 key recommendations in the policy update:

1. Germ-line Implications of Somatic Mutation Profiling

ASCO recommends additional research to generate best practices for providing patients with incidental and secondary germ-line information. Additionally, the Society has stressed the need for knowledge gain on patient preferences, optimal pretest education and informed consent, and multilevel outcomes (ie, patient, provider, healthcare system delivery, and cost). If patients choose not to receive germ-line findings, ASCO recommends that testing laboratories should have protocols to report only the somatic mutational data.

2. Multigene Panel Testing for Cancer Susceptibility

Recognizing the level of detailed information that multigene panels provide, ASCO acknowledges that these tests may provide information on variants of uncertain significance. Due to existing knowledge gaps, ASCO recommends that providers with particular expertise in cancer risk assessment should be involved in the ordering and interpretation of multigene panels that include genes of uncertain clinical utility and genes not suggested by the patient's personal and/or family history. Development of evidence-based guidelines for optimal use of these multigene panels and provider education are also encouraged.

3. Quality Assurance in Genetic Testing

Emphasizing the need for risk-based FDA regulation of laboratory-developed tests as well as commercial diagnostic tests, ASCO underscores the importance of innovation and patient access for these tests.

4. Education for Oncology Professionals

ASCO recommends that healthcare providers involved in cancer risk assessment should participate in oncology training programs and continued education programs. New trainees should receive adequate training to be able to achieve necessary risk-assessment skills.

5. Access to Cancer Genetic Services

Coverage policies can ensure patient access to these innovative cancer risk-assessment tools, and ASCO has called for coverage assurance for individuals who are suspected to be at increased genetic risk. Additionally, ASCO opposes payment policies that could potentially negatively impact the care of patients with cancer by serving as barriers to the appropriate use of genetic testing services. **EBO**

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Topics

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- Next-Generation Genetic Sequencing (Genomics 101) for Payers
- Outcomes from Mandatory Genetic Testing and Counseling Programs
- ***Panel:*** The Impact of FDA Regulation on Diagnostics in Oncology

Session 2: Genomics in Oncology, Part 2 — Precision Medicine

- How the President's Precision Medicine Initiative Will Learn From Oncology Practice
- The Patient Lens on Precision Medicine
- ***Panel:*** Reimbursement Challenges for Oncology Innovations: Who Pays?

Session 3: The Future of Immuno-oncology

- Are We Close to the Big "C": Cure?
- Evaluation of Options and Outcomes in a "Me Too" Market
- ***Panel:*** The Role of PBMs in Managing High-Cost Treatment Options

Session 4: Innovations for Patient-Centered Care

- Updates in Big Data for Oncology: What Are We Learning?
- Payment Models in Oncology Care at the Patient Level
- ***Panel:*** Navigating the Conflict of Personalized Medicine vs Population Management

Session 5: Accountable Care in Oncology

- ***Panel:*** Evolution of the ACO Model to Meet the Needs of Oncology Patients and Payers

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FDA UPDATES

FDA Grants Priority Review for Alectinib in Advanced NSCLC Resistant to Crizotinib

SURABHI DANGI-GARIMELLA, PHD

Roche has announced[1] that an oral anaplastic lymphoma kinase (ALK) inhibitor developed by the company has been granted priority review by the US regulatory authority. The company filed a New Drug Application (NDA) for alectinib (Alecensa) within 2 years of being granted a Breakthrough Therapy designation for the treatment of patients with ALK-positive, locally advanced or metastatic non-small cell lung cancer (NSCLC) who have progressed or are intolerant to crizotinib.

Alectinib was approved in Japan last year for the treatment of patients with

ALK-positive NSCLC based on the results of a phase 1/2 study that included individuals whose tumors had advanced, were recurrent, or were unresectable. The 90% response rate in the Japanese population may have led to the drug's approval based on early phase results.[2]

The NDA filed with the FDA provides results of two phase 2 studies. One was a single-arm, open-label, multicenter trial (NP28761) evaluating the safety and efficacy of alectinib in 87 individuals with ALK-positive NSCLC whose disease progressed on crizotinib. Nearly 50% of trial participants saw their tumors shrink. Those with metastases to the brain or other regions of the central nervous system (CNS) also saw their cancer respond to alectinib, indicating that the drug crosses the blood–brain barrier, a lipid-rich region which is usually difficult to penetrate. The duration of primary tumor response was sustained for a median period of 7.5 months. Most common grade 3 or greater adverse events in the trial were dyspnea and increased levels of muscle and liver enzymes.

A second trial (NP28673) evaluated the safety and efficacy of alectinib in 138 individuals with a similar profile compared with NP28761. Using RECIST criteria, a 50% response rate was observed with

respect to tumor shrinkage in this population. Although the median duration of response was longer in this group (11.2 months), a CNS response in those with brain and other CNS metastases was observed. Dyspnea was the most common grade 3 or higher adverse event observed in NP28673.

Sales discussions around the drug began immediately following approval in Japan, with experts predicting a blockbuster status for alectinib. Analysts at Cowen and Company project the drug could bring in annual sales of $1 billion by 2020.[3]

The decision date for alectinib for US approval is set for March 4, 2016. **EBO**

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1. FDA grants Roche's alectinib Priority Review for specific type of ALK-positive lung cancer. http://www.roche.com/investors/updates/inv-update-2015-09-09.htm. Published and accessed September 9, 2015.

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Medical World News®

FDA UPDATES

Opdivo-Yervoy Approved for Metastatic Melanoma Harboring Wild-Type *BRAF*

In a press release[1] published on October 1, 2015, Bristol-Myers Squibb (BMS) announced the approval of its combination regimen of 2 immuno-oncology agents, nivolumab (Opdivo) and ipilimumab (Yervoy), for patients with *BRAF V600* wild-type metastatic melanoma.

This approval marks the first-ever approval of 2 immuno-oncology agents in cancer treatment. According to the FDA,[2] the approval was based on objective response rate, prolonged duration of response, and improvement in progression free survival—outcomes from the CheckMate-069 trial in 142 treatment-

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Brief Summary of Prescribing Information.

INDICATIONS AND USAGE
ZYTIGA is a CYP17 inhibitor indicated in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer.

CONTRAINDICATIONS
Pregnancy: ZYTIGA can cause fetal harm when administered to a pregnant woman. ZYTIGA is not indicated for use in women. ZYTIGA is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus and the potential risk for pregnancy loss *[see Use in Specific Populations]*.

WARNINGS AND PRECAUTIONS
Hypertension, Hypokalemia and Fluid Retention Due to Mineralocorticoid Excess: ZYTIGA may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition *[see Clinical Pharmacology (12.1) in full Prescribing Information]*. In the two randomized clinical trials, grade 3 to 4 hypertension occurred in 2% of patients, grade 3 to 4 hypokalemia in 4% of patients, and grade 3 to 4 edema in 1% of patients treated with ZYTIGA *[see Adverse Reactions]*.

Co-administration of a corticosteroid suppresses adrenocorticotropic hormone (ACTH) drive, resulting in a reduction in the incidence and severity of these adverse reactions. Use caution when treating patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalemia or fluid retention, e.g., those with heart failure, recent myocardial infarction or ventricular arrhythmia. Use ZYTIGA with caution in patients with a history of cardiovascular disease. The safety of ZYTIGA in patients with left ventricular ejection fraction <50% or New York Heart Association (NYHA) Class III or IV heart failure (in Study 1) or NYHA Class II to IV heart failure (in Study 2) was not established because these patients were excluded from these randomized clinical trials *[see Clinical Studies (14) in full Prescribing Information]*. Monitor patients for hypertension, hypokalemia, and fluid retention at least once a month. Control hypertension and correct hypokalemia before and during treatment with ZYTIGA.

Adrenocortical Insufficiency: Adrenal insufficiency occurred in the two randomized clinical studies in 0.5% of patients taking ZYTIGA and in 0.2% of patients taking placebo. Adrenocortical insufficiency was reported in patients receiving ZYTIGA in combination with prednisone, following interruption of daily steroids and/or with concurrent infection or stress. Use caution and monitor for symptoms and signs of adrenocortical insufficiency, particularly if patients are withdrawn from prednisone, have prednisone dose reductions, or experience unusual stress. Symptoms and signs of adrenocortical insufficiency may be masked by adverse reactions associated with mineralocorticoid excess seen in patients treated with ZYTIGA. If clinically indicated, perform appropriate tests to confirm the diagnosis of adrenocortical insufficiency. Increased dosage of corticosteroids may be indicated before, during and after stressful situations *[see Warnings and Precautions]*.

Hepatotoxicity: In the two randomized clinical trials, grade 3 or 4 ALT or AST increases (at least 5X ULN) were reported in 4% of patients who received ZYTIGA, typically during the first 3 months after starting treatment. Patients whose baseline ALT or AST were elevated were more likely to experience liver test elevation than those beginning with normal values. Treatment discontinuation due to liver enzyme increases occurred in 1% of patients taking ZYTIGA. No deaths clearly related to ZYTIGA were reported due to hepatotoxicity events.

Measure serum transaminases (ALT and AST) and bilirubin levels prior to starting treatment with ZYTIGA, every two weeks for the first three months of treatment and monthly thereafter. In patients with baseline moderate hepatic impairment receiving a reduced ZYTIGA dose of 250 mg, measure ALT, AST, and bilirubin prior to the start of treatment, every week for the first month, every two weeks for the following two months of treatment and monthly thereafter. Promptly measure serum total bilirubin, AST, and ALT if clinical symptoms or signs suggestive of hepatotoxicity develop. Elevations of AST, ALT, or bilirubin from the patient's baseline should prompt more frequent monitoring. If at any time AST or ALT rise above five times the ULN, or the bilirubin rises above three times the ULN, interrupt ZYTIGA treatment and closely monitor liver function.

Re-treatment with ZYTIGA at a reduced dose level may take place only after return of liver function tests to the patient's baseline or to AST and ALT less than or equal to 2.5X ULN and total bilirubin less than or equal to 1.5X ULN *[see Dosage and Administration (2.2) in full Prescribing Information]*.

The safety of ZYTIGA re-treatment of patients who develop AST or ALT greater than or equal to 20X ULN and/or bilirubin greater than or equal to 10X ULN is unknown.

ADVERSE REACTIONS
The following are discussed in more detail in other sections of the labeling:
- Hypertension, Hypokalemia, and Fluid Retention due to Mineralocorticoid Excess *[see Warnings and Precautions]*.
- Adrenocortical Insufficiency *[see Warnings and Precautions]*.
- Hepatotoxicity *[see Warnings and Precautions]*.

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Clinical Trial Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Two randomized placebo-controlled, multicenter clinical trials enrolled patients who had metastatic castration-resistant prostate cancer who were using a gonadotropin-releasing hormone (GnRH) agonist or were previously treated with orchiectomy. In both Study 1 and Study 2 ZYTIGA was administered at a dose of 1,000 mg daily in combination with prednisone 5 mg twice daily in the active treatment arms. Placebo plus prednisone 5 mg twice daily was given to control patients.

The most common adverse drug reactions (≥10%) reported in the two randomized clinical trials that occurred more commonly (>2%) in the abiraterone acetate arm were fatigue, joint swelling or discomfort, edema, hot flush, diarrhea, vomiting, cough, hypertension, dyspnea, urinary tract infection and contusion.

The most common laboratory abnormalities (>20%) reported in the two randomized clinical trials that occurred more commonly (≥2%) in the abiraterone acetate arm were anemia, elevated alkaline phosphatase, hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycemia, elevated AST, hypophosphatemia, elevated ALT and hypokalemia.

Study 1: Metastatic CRPC Following Chemotherapy: Study 1 enrolled 1195 patients with metastatic CRPC who had received prior docetaxel chemotherapy. Patients were not eligible if AST and/or ALT ≥2.5X ULN in the absence of liver metastases. Patients with liver metastases were excluded if AST and/or ALT >5X ULN.

Table 1 shows adverse reactions on the ZYTIGA arm in Study 1 that occurred with a ≥2% absolute increase in frequency compared to placebo or were events of special interest. The median duration of treatment with ZYTIGA was 8 months.

Table 1: Adverse Reactions due to ZYTIGA in Study 1

	ZYTIGA with Prednisone (N=791)		Placebo with Prednisone (N=394)	
System/Organ Class	All Grades[1]	Grade 3-4	All Grades	Grade 3-4
Adverse reaction	%	%	%	%
Musculoskeletal and connective tissue disorders				
Joint swelling/ discomfort[2]	29.5	4.2	23.4	4.1
Muscle discomfort[3]	26.2	3.0	23.1	2.3
General disorders				
Edema[4]	26.7	1.9	18.3	0.8
Vascular disorders				
Hot flush	19.0	0.3	16.8	0.3
Hypertension	8.5	1.3	6.9	0.3
Gastrointestinal disorders				
Diarrhea	17.6	0.6	13.5	1.3
Dyspepsia	6.1	0	3.3	0
Infections and infestations				
Urinary tract infection	11.5	2.1	7.1	0.5
Upper respiratory tract infection	5.4	0	2.5	0
Respiratory, thoracic and mediastinal disorders				
Cough	10.6	0	7.6	0
Renal and urinary disorders				
Urinary frequency	7.2	0.3	5.1	0.3
Nocturia	6.2	0	4.1	0
Injury, poisoning and procedural complications				
Fractures[5]	5.9	1.4	2.3	0
Cardiac disorders				
Arrhythmia[6]	7.2	1.1	4.6	1.0
Chest pain or chest discomfort[7]	3.8	0.5	2.8	0
Cardiac failure[8]	2.3	1.9	1.0	0.3

naïve patients with unresectable or metastatic melanoma. The trial showed a statistically significant increase in confirmed objective response rate in 95 patients with melanoma expressing wild-type *BRAF* treated with the combination (60%; 95% confidence interval (CI), 48-71; *P*<.001), compared with ipilimumab and placebo (47 patients) (11%; 95% CI, 3-25). Nearly 17% of patients treated with the combination had a complete response, while 43% had a partial response.

A 60% reduction in the risk of progression was observed with the combination treatment compared with ipilimumab alone (Hazard ratio = 0.40; 95% CI: 0.22-0.71; *P*<.002). Median survival improved by more than 4 months with the combination, 8.9 months compared with 4.7 months seen with the ipilimumab-treated cohort.

The combination was, however, responsible for more serious adverse events (62% vs 39%), adverse reactions leading to permanent discontinuation (43% vs 11%) or dose delay (47% vs 2%), and grade 3 or 4 adverse reactions (69% vs 43%). The most frequent serious adverse reactions in patients receiving the combination were colitis (17%), diarrhea (9%), pyrexia (6%), and pneumonitis (5%). Additional clinically significant

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[1] Adverse events graded according to CTCAE version 3.0
[2] Includes terms Arthritis, Arthralgia, Joint swelling, and Joint stiffness
[3] Includes terms Muscle spasms, Musculoskeletal pain, Myalgia, Musculoskeletal discomfort, and Musculoskeletal stiffness
[4] Includes terms Edema, Edema peripheral, Pitting edema, and Generalized edema
[5] Includes all fractures with the exception of pathological fracture
[6] Includes terms Arrhythmia, Tachycardia, Atrial fibrillation, Supraventricular tachycardia, Atrial tachycardia, Ventricular tachycardia, Atrial flutter, Bradycardia, Atrioventricular block complete, Conduction disorder, and Bradyarrhythmia
[7] Includes terms Angina pectoris, Chest pain, and Angina unstable. Myocardial infarction or ischemia occurred more commonly in the placebo arm than in the ZYTIGA arm (1.3% vs. 1.1% respectively).
[8] Includes terms Cardiac failure, Cardiac failure congestive, Left ventricular dysfunction, Cardiogenic shock, Cardiomegaly, Cardiomyopathy, and Ejection fraction decreased

Table 2 shows laboratory abnormalities of interest from Study 1. Grade 3-4 low serum phosphorus (7%) and low potassium (5%) occurred at a greater than or equal to 5% rate in the ZYTIGA arm.

Table 2: Laboratory Abnormalities of Interest in Study 1

	Abiraterone (N=791)		Placebo (N=394)	
Laboratory Abnormality	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Hypertriglyceridemia	62.5	0.4	53.0	0
High AST	30.6	2.1	36.3	1.5
Hypokalemia	28.3	5.3	19.8	1.0
Hypophosphatemia	23.8	7.2	15.7	5.8
High ALT	11.1	1.4	10.4	0.8
High Total Bilirubin	6.6	0.1	4.6	0

Study 2: Metastatic CRPC Prior to Chemotherapy: Study 2 enrolled 1088 patients with metastatic CRPC who had not received prior cytotoxic chemotherapy. Patients were ineligible if AST and/or ALT ≥2.5X ULN and patients were excluded if they had liver metastases.

Table 3 shows adverse reactions on the ZYTIGA arm in Study 2 that occurred with a ≥2% absolute increase in frequency compared to placebo. The median duration of treatment with ZYTIGA was 13.8 months.

Table 3: Adverse Reactions in ≥5% of Patients on the ZYTIGA Arm in Study 2

	ZYTIGA with Prednisone (N=542)		Placebo with Prednisone (N=540)	
System/Organ Class Adverse reaction	All Grades[1] %	Grade 3-4 %	All Grades %	Grade 3-4 %
General disorders				
Fatigue	39.1	2.2	34.3	1.7
Edema[2]	25.1	0.4	20.7	1.1
Pyrexia	8.7	0.6	5.9	0.2
Musculoskeletal and connective tissue disorders				
Joint swelling/ discomfort[3]	30.3	2.0	25.2	2.0
Groin pain	6.6	0.4	4.1	0.7
Gastrointestinal disorders				
Constipation	23.1	0.4	19.1	0.6
Diarrhea	21.6	0.9	17.8	0.9
Dyspepsia	11.1	0.0	5.0	0.2
Vascular disorders				
Hot flush	22.3	0.2	18.1	0.0
Hypertension	21.6	3.9	13.1	3.0
Respiratory, thoracic and mediastinal disorders				
Cough	17.3	0.0	13.5	0.2
Dyspnea	11.8	2.4	9.6	0.9
Psychiatric disorders				
Insomnia	13.5	0.2	11.3	0.0
Injury, poisoning and procedural complications				
Contusion	13.3	0.0	9.1	0.0
Falls	5.9	0.0	3.3	0.0
Infections and infestations				
Upper respiratory tract infection	12.7	0.0	8.0	0.0
Nasopharyngitis	10.7	0.0	8.1	0.0

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Table 3: Adverse Reactions in ≥5% of Patients on the ZYTIGA Arm in Study 2 (continued)

	ZYTIGA with Prednisone (N=542)		Placebo with Prednisone (N=540)	
System/Organ Class Adverse reaction	All Grades[1] %	Grade 3-4 %	All Grades %	Grade 3-4 %
Renal and urinary disorders				
Hematuria	10.3	1.3	5.6	0.6
Skin and subcutaneous tissue disorders				
Rash	8.1	0.0	3.7	0.0

[1] Adverse events graded according to CTCAE version 3.0
[2] Includes terms Edema peripheral, Pitting edema, and Generalized edema
[3] Includes terms Arthritis, Arthralgia, Joint swelling, and Joint stiffness

Table 4 shows laboratory abnormalities that occurred in greater than 15% of patients, and more frequently (>5%) in the ZYTIGA arm compared to placebo in Study 2. Grade 3-4 lymphopenia (9%), hyperglycemia (7%) and high alanine aminotransferase (6%) occurred at a greater than 5% rate in the ZYTIGA arm.

Table 4: Laboratory Abnormalities in >15% of Patients in the ZYTIGA Arm of Study 2

	Abiraterone (N=542)		Placebo (N=540)	
Laboratory Abnormality	Grade 1-4 %	Grade 3-4 %	Grade 1-4 %	Grade 3-4 %
Hematology				
Lymphopenia	38.2	8.7	31.7	7.4
Chemistry				
Hyperglycemia[1]	56.6	6.5	50.9	5.2
High ALT	41.9	6.1	29.1	0.7
High AST	37.3	3.1	28.7	1.1
Hypernatremia	32.8	0.4	25.0	0.2
Hypokalemia	17.2	2.8	10.2	1.7

[1]Based on non-fasting blood draws

Cardiovascular Adverse Reactions: In the combined data for studies 1 and 2, cardiac failure occurred more commonly in patients treated with ZYTIGA compared to patients on the placebo arm (2.1% versus 0.7%). Grade 3-4 cardiac failure occurred in 1.6% of patients taking ZYTIGA and led to 5 treatment discontinuations and 2 deaths. Grade 3-4 cardiac failure occurred in 0.2% of patients taking placebo. There were no treatment discontinuations and one death due to cardiac failure in the placebo group.

In Study 1 and 2, the majority of arrhythmias were grade 1 or 2. There was one death associated with arrhythmia and one patient with sudden death in the ZYTIGA arms and no deaths in the placebo arms. There were 7 (0.5%) deaths due to cardiorespiratory arrest in the ZYTIGA arms and 3 (0.3%) deaths in the placebo arms. Myocardial ischemia or myocardial infarction led to death in 3 patients in the placebo arms and 2 deaths in the ZYTIGA arms.

Post Marketing Experience

The following additional adverse reactions have been identified during post approval use of ZYTIGA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Respiratory, Thoracic and Mediastinal Disorders: non-infectious pneumonitis.

Musculoskeletal and Connective Tissue Disorders: myopathy, including rhabdomyolysis.

DRUG INTERACTIONS

Drugs that Inhibit or Induce CYP3A4 Enzymes: Based on *in vitro* data, ZYTIGA is a substrate of CYP3A4.

In a dedicated drug interaction trial, co-administration of rifampin, a strong CYP3A4 inducer, decreased exposure of abiraterone by 55%. Avoid concomitant strong CYP3A4 inducers during ZYTIGA treatment. If a strong CYP3A4 inducer must be co-administered, increase the ZYTIGA dosing frequency *[see Dosage and Administration (2.3)* and *Clinical Pharmacology (12.3) in full Prescribing Information]*.

In a dedicated drug interaction trial, co-administration of ketoconazole, a strong inhibitor of CYP3A4, had no clinically meaningful effect on the pharmacokinetics of abiraterone *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Effects of Abiraterone on Drug Metabolizing Enzymes: ZYTIGA is an inhibitor of the hepatic drug-metabolizing enzymes CYP2D6 and CYP2C8. In

immune-mediated adverse reactions included pneumonitis, hepatitis, endocrinopathies, nephritis/renal dysfunction, and rash.

"Today's approval of the Opdivo + Yervoy Regimen marks another first for our research in Immuno-Oncology and represents our unwavering commitment to continually redefine cancer care, and offer patients new treatment options with the goal of improved outcomes," said Giovanni Caforio, CEO of BMS. **EBO**

References

1. Bristol-Myers Squibb Receives Approval from the U.S. Food and Drug Administration for the Opdivo (nivolumab) + Yervoy (ipilimumab) Regimen in BRAF V600 Wild-Type Unresectable or Metastatic Melanoma [press release]. Princeton, NJ: Bristol-Myers Squibb; October 1, 2015. http://news.bms.com/press-release/bristol-myers-squibb-receives-approval-us-food-and-drug-administration-opdivo-nivoluma.

2. Nivolumab in combination with ipilimumab. FDA website. http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm465274.htm. Published and accessed October 1, 2015.

Elotuzumab Accepted for Priority Review by FDA for Previously Treated Patients With Multiple Myeloma

SURABHI DANGI-GARIMELLA, PHD

The FDA has accepted elotuzumab, being developed as Empliciti, for priority review.[1] A monoclonal antibody that stimulates the signaling lymphocyte activation molecule F7 (SLAMF7) cell-surface receptor, the biologics license application for elotuzumab was submitted jointly by Bristol-Myers Squibb and AbbVie for the treatment of multiple myeloma in patients who have received one or more prior therapies.

The submission primarily includes results from the ongoing ELOQUENT-2 trial, a phase-3, open-label, multicenter global study that included 646 patients at 168 sites who were randomized to receive elotuzumab in combination with lenalidomide and dexamethasone (elotuzumab group) or lenalidomide and dexamethasone alone (control group) in 28-day cycles until disease progression, unacceptable toxicity, or withdrawal of consent. Primary end points of the trial, results of which were published in the *New England Journal of Medicine*,[2] were progression-free survival (PFS) and overall response rate (ORR). Secondary end points were overall survival (OS) and severity of pain or interference with daily life.

At a median follow-up of 24.5 months, 35% of patients in the elotuzumab group and 20% in the control group were receiving study treatment. PFS at 1 year was 68% (95% confidence interval [CI], 0.63-0.73) in the elotuzumab group and 57% (95% CI, 0.51-0.62) in the control group. Median PFS in the elotuzumab group was 19.4 months (95% CI, 0.16-0.22) compared with 14.9 months (95% CI, 0.12-0.17) in the control group, with a hazard ratio of 0.70 (95% CI, 0.57-0.85; P <.001).

The authors concluded that in patients with relapsed or refractory multiple myeloma, the addition of elotuzumab to lenalidomide and dexamethasone, compared with lenalidomide and dexamethasone as control therapy, improved PFS and ORR, showing that direct activation and engagement of the innate immune system to selectively kill myeloma cells can provide clinically meaningful and statistically significant improvements in treatment outcomes. The elotuzumab group presented a 30% reduction in disease progression or death compared with the control group. OS studies are ongoing.

Results from a phase 2 open-label study, which were presented[3] at the annual meeting of the American Society of Clinical Oncology in May this year, were also a part of the submission to the FDA. The study evaluated the advantage of adding elotuzumab to a treatment regimen of bortezomib and dexamethasone in patients with relapsed-refractory multiple myeloma. Results presented showed that the study met its primary end point of PFS: elotuzumab significantly improved PFS when combined with bortezomib and dexamethasone, and elotuzumab-treated patients had a 28% reduction in their risk of disease progression. Elotuzumab is simultaneously undergoing accelerated assessment in Europe.

"Bristol-Myers Squibb is delighted by the approach both agencies have taken to review the Empliciti applications as it underscores the unmet medical need in the treatment of multiple myeloma and the role immuno-oncology may play," said Michael Giordano, MD, senior vice president, head of oncology development, Bristol-Myers Squibb, in a press release.[1] "The acceptance of our applications by the FDA and EMA [European Medicines Agency] brings Bristol-Myers Squibb's immuno-oncology science a step closer to helping patients with hematologic malignancies." **EBO**

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Molecularly Targeted SHIVA Trial Fails to Improve Outcomes in Refractory Cancer Patients

SURABHI DANGI-GARIMELLA, PHD

Bioinformatics has opened up multiple avenues for researchers. Next generation clinical trials are moving away from histology-based tumor classification and directing their attention to the genetic and proteomic profile of the tumor. The results of one such proof-of-concept trial, conducted at academic centers in France, have now been published in *The Lancet Oncology*.[1] The SHIVA trial, which assessed the clinical efficacy of molecularly targeted agents being marketed in the country outside of their indications, failed to improve progression-free survival (PFS) with off-label use compared with treatment per physician's choice.

The trial was designed as an open-label, randomized, controlled phase 2, with participants that included adult patients with metastatic solid tumor refractory to standard of care. The primary criteria for inclusion were:

- Eastern Cooperative Oncology Group performance status of 0 or 1
- disease that was accessible for a biopsy or resection of a metastatic site
- at least 1 measurable lesion.

Of the 741 patients screened, only those with alterations in the hormone receptor pathway, PI3K/AKT/mTOR pathway, or the RAF/MEK pathway were included in the trial. The patients could be matched to 1 of 10 regimens (erlotinib, lapatinib plus trastuzumab, sorafenib, imatinib, dasatinib, vemurafenib, everolimus, abiraterone, letrozole, tamoxifen). Eligible patients (195) were randomly assigned to an experimental group, to receive a matched molecularly targeted agent (99) and a control group that received treatment at physician's choice (96). Median follow-up was 11.3 months (range, 5.8 to 11.6 months) in the experimental group and 11.3 months (range 8.1 months to 11.6 months) in the control group.

The median PFS observed was 2.3 months (95% confidence interval (CI), 1.7-3.8) in the experimental group versus 2 months in the control group (95% CI, 0.65-1.19; P = .41). In the safety studies, 43% of patients in the experimental group and 35% of patients in the control group (administered cytotoxic chemotherapy) had grade 3 to 4 adverse events. Based on their results, the authors conclude that off-label indications for molecularly targeted agents should be discouraged.

However, Richard Schilsky, MD, chief medical officer of the American Society of Clinical Oncology, said in an interview that results of the SHIVA study are important because it tells us "that we need to continue doing research in this area of personalized medicine." He thinks that at this early stage though, such studies should be conducted under the umbrella of a clinical trial.[2]

A similar trial was recently launched in the United States. The National Cancer Institute's MATCH trial will evaluate between 10 and 15 molecularly targeted agents in patients grouped based on tumor type or genetic abnormality.[3] **EBO**

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Medical World News®

MANAGED CARE UPDATES

ASCO Submits Comments on the Proposed Medicare Physician Fee Schedule Rules

SURABHI DANGI-GARIMELLA, PHD

In July of this year, CMS made public proposed policy changes to the Medicare Physician Fee Schedule,[1] with updates on payment policies, payment rates, and quality provisions. These are the first set of proposed changes after the Sustainable Growth Rate repeal and include important changes to the Physician Quality Reporting System (PQRS), the Physician Value-Based Payment Modifier, and the Medicare Electronic Health Record Incentive Program.

In response, the American Society of Clinical Oncology (ASCO) submitted a letter to CMS at the end of the public comment period recommending that CMS should "reconsider revisions to payment policies that could be administratively burdensome to oncology practices and result in reimbursement that inadequately supports optimal cancer patient care."

Although agreeing with some of the policy changes, ASCO drew attention to certain provisions that would impact patient care, physician payment, and quality of care. The following are concerns of and recommendations from the organization:

1. **"Incident" to billing.** ASCO recommends that CMS should not implement its proposal to change the "incident" to rules without clarifying that the ordering physician may differ from the supervising physician for chemotherapy administration.
2. **Potentially misvalued codes.** ASCO recommends that CMS should use methodologies other than the "high expenditure by specialty screen" to identify potentially misvalued codes.
3, **Cancer staging measure.** ASCO recommends that CMS should not finalize its proposal to eliminate the cancer staging measure from registry reporting in the PQRS. ASCO urges CMS to retain this measure and consider refining it to apply only to a period of time following the initial office visit.
4. **Chronic care management.** ASCO recommends that chronic care management services have the potential to provide meaningful opportunities to improve oncology care management and lower Medicare's overall expenditures. CMS should continue to focus resources on providing beneficiaries with access to medical advice and eliminating counterproductive administrative burdens on providers that hamper patient access.

Additionally, ASCO has urged CMS to reconsider the valuation of radiation oncology services to allow continuous patient access, particularly in community clinics. For biosimilar products, ASCO has proposed fair and adequate reimbursement by CMS to allow patient access to these biologicals at a lower cost. The letter applauds the CMS proposal to provide reimbursement for advance care planning with the flexibility of seeking advice from multiple providers. ASCO has recommended that CMS should establish new codes and payments for cognitive services performed in oncology care, which CMS has recognized as an important task performed by specialists who care for certain subsets of Medicare beneficiaries. Other suggestions address tailoring quality and value measures for oncology and implementing alternate payment models to improve quality while reducing cost of care. **EBO**

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CMS Changes to Physician Fee Schedule Face Resistance From Radiation Oncologists

SURABHI DANGI-GARIMELLA, PHD

Although the comment period for the Medicare Physician Fee Schedule (MPFS)[1] for 2016 ended September 8, 2015, physicians have not held back in expressing concerns and their opposition to some of the provisions within the MPFS. The main opposition comes from community oncology centers and freestanding cancer care facilities who would feel the greatest impact from the proposed cuts. According to the proposal, there would be a 3% overall reduction in payments to radiation oncology specialists, although the cuts would vary depending on the patient population and could even reach 10%.

Some of the proposed changes by CMS for radiation oncology include:

- The implementation of new treatment delivery codes that were delayed in the calendar year 2016 PFS Final Rule, as well as CMS modifications to those codes
- CMS's proposal to increase the equipment utilization assumption for the linear accelerator from 50% to 70%
- Corresponding increases in other radiation oncology codes due to an increase in the indirect practice cost index.

Immediately after the policy and payment changes were proposed, the American Society for Radiation Oncology (ASTRO) issued a press release expressing concern over the cuts. "The implementation of these 3 dramatic policy changes at once represents too much, too fast for community-based clinics to absorb and could have devastating effects, particularly for those centers in rural and underserved areas," said ASTRO Chair Bruce G. Haffty, MD, FASTRO, in the release.

In a related blog on *The Hill*,[2] Christopher M. Rose, MD, chief technology officer at Vantage Oncology, Inc—a coalition of 296 freestanding cancer care facilities across 35 states—wrote that the proposed changes could have devastating effects on care delivery and patient access, especially the more vulnerable populations. "If the proposed PFS changes were adopted, the payments for a course of care for prostate and breast cancer will be reduced by 25% and 19%, respectively. Furthermore, this same care will be reimbursed 36% less and 32% less, respectively, in the freestanding setting than care delivered in the hospital setting," he writes.

The final rule is expected to be issued by November 1, 2015, and will become effective January 1, 2016. **EBO**

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Medical World News®
MANAGED CARE UPDATES

Cancer Drugs Driving 340B Growth Even More Than Understood, Report Finds

MARY K. CAFFREY

The discount drug program intended for safety-net hospitals and AIDS clinics has mushroomed even more than earlier reports suggested, with oncology drugs fueling much of the growth, according to a new report commissioned by community oncology providers.[1]

An examination of Medicare Part B hospital outpatient spending shows that 340B institutions accounted for 58% of all spending on drug payments in 2013, with oncology drugs making up 40% of the Medicare fee-for-service costs. The study, by Aaron Vandervelde of the Berkeley Research Group of Washington, DC, was sponsored by the Community Oncology Alliance (COA), which has sounded the alarm about unrestrained 340B growth in recent years.

Figures from 2010 through 2013 reveal explosive growth in cancer drug spending in the 340B sector: Medicare Part B reimbursement rose 123% for oncology drugs in this period compared with 31% for non-340B hospitals and a 5% decrease for community oncology practices. Medicaid expansion may only exacerbate these trends if there are no changes to the program, according to the report.

Cancer drugs have become "the pot of gold at the end of the rainbow," for 340B hospitals, said Ted Okon, MBA, executive director of COA, in an interview with *Evidence-Based Oncology*. Okon said the report underscores 2 key problems: it's too easy for hospitals to qualify for the program and hospitals have powerful financial incentives to buy up oncology practices, so these financial strategies can proliferate at sites beyond the hospital walls.

The original purpose of 340B was noble: hospitals caring for patients who may be uninsured or underinsured can buy drugs at discounts of 20% to 50%, but charge full price to those able to pay or to their insurer, which can include Medicare or Medicaid. However, if this practice extends to oncology practices owned by the hospital, the ability to buy discounted drugs and charge insurers a higher price does many things at once.

First, it forces independent oncology practices to compete with hospital-owned providers when they lack access to similar discounts; many are compelled to either join with the hospital or go out of business. Second, Okon explained, the ever-increasing pool of providers buying "discounted" drugs means those rebates have to be built into the overall price, which has contributed to trends in oncology costs seen today. "Already, 340B expansion has had unintended consequences," Okon said. "Anyone who doesn't think all these rebates are not fueling drug prices is not paying attention."

Although a July report by the Government Accounting Office (GAO) found that the 340B program had created perverse incentives for hospitals to prescribe more drugs and more expensive drugs, its finding that 40% of hospitals were enrolled did not fully capture the scope of recent growth. By looking at actual spending on prescriptions instead of comparing 340B and non-340B hospitals, Okon said, the report shows that "the big growth is on the hospital side, not the grantee side"; the latter group includes federally qualified health centers and Ryan White HIV/AIDS Centers. In addition, spending on cancer drugs appears to be a business strategy among the 340B hospitals; left unchecked, this will only encourage more program growth, with consequences for all payers, Medicare and Medicaid, and patients who will face a combination of higher co-payments and fewer care options in their communities.

The report stated, "Oncology drug reimbursement has increased by 86% at continuously enrolled 340B hospitals and 58% at non-340B hospitals. Although some of this growth is a function of changing demographics and advancements in chemotherapy (which typically come with an increased cost), the disparity in growth rates between 340B and non-340B hospitals speaks to the disproportionate role that 340B hospitals play in the acquisition of community oncology practices."

"This is, in large part," the report concluded, "a function of the sizeable profits that 340B hospitals realize on Medicare and commercial reimbursement of oncology drugs."

Among the report's findings:

- The 340B program grows each year. In 2010, there were 89 new hospitals enrolled that qualified as "Disproportionate Share," or DSH, along with 342 non-DSH. A hospital's DSH status is calculated based on whether patients qualify for Medicare Part A, Medicaid, or Supplemental Security Income. The number of new enrollees rose for each until 2014 brought 324 new DSH enrollees and 1222 non-DSH and other specialized clinics.
- The report found that new enrollees—those arriving in 2010 or later—accounted for 23% of Medicare Part B outpatient drug spending in 2013.
- Medicare spending in 2013 on oncology drugs in 340B hospitals outpaced that of non-340B hospitals—$3.064 billion vs $2.672 billion—even though overall hospital revenues are higher among the non-340B hospitals: $1.968 trillion vs $1.411 trillion for 340B.
- The gap in spending per beneficiary in Medicare Part B fee-for-service for oncology drugs between 340B hospitals and community oncology practices is large and growing: in 2010, 340B hospitals spent $1722 per patient per day while community practices spent $1226. In 2013, the per-patient, per-day figure had grown to $1920 for 340B hospitals but barely budged for community practices, to $1266, at a time when the cost of cancer drugs is soaring.

The report confirms the overall conclusions of the GAO findings. The agency said, "While it is not unlawful for hospitals to benefit financially from the drug discount program," such practices are "not consistent with the legislative intent of the 340B program." It noted that taxpayers, generally, and patients, individually, suffer harm, since Medicare Part B beneficiaries are responsible for a 20% co-payment, which will rise along with drug prices. That report also questioned whether all healthcare provided in 340B hospitals is appropriate, stating, "Absent a change in financial incentives, potentially inappropriate spending on drugs may continue."

The report comes as the Health Resources and Services Administration (HRSA)[2] takes comment on a proposed guidance that would increase oversight and double the number of conditions needed to qualify for 340B status. Some hospital groups have questioned whether the rules will simply make oncology care more bureaucratic and inconvenient for patients, and whether limits on access will result.

"The 340B program is very administratively complex and costly to administer now," Beth Feldpush, senior vice president of advocacy and policy for America's Essential Hospitals, said when the guidance was issued. "For our members that rely on the savings, I could see where if HRSA narrowed the program so much, a hospital could say the costs to run this program may outweigh (the benefit of) participation in it."

Comment on the guidance continues through October 27, 2015. **EBO**

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Tips for Caring for Patients Who Have Been Treated for Childhood Cancer
(CONTINUED FROM COVER)

ABOUT THE AUTHOR

LISA DILLER, MD

Dr Diller is chief medical officer of Dana-Farber/Boston Children's Cancer and Blood Disorders Center and director of the David B. Perini Jr. Quality of Life Clinic for survivors of childhood cancer.

Refer your patient for a one-time consultation [to a survivor care clinic], during which a treatment summary and survivorship care plan can be created based on a careful review of the patient's records and discussion with the patient and, sometimes, the parent. For adults who were treated as children and know little about their cancer history, this process gives them important information.

tain one, as well as a survivorship plan, from the treating oncology center. If this is not possible, most major cancer centers and hospitals that treat pediatric cancer have clinics where survivors can be seen well into adulthood. Refer your patient for a one-time consultation, during which a treatment summary and survivorship care plan can be created based on a careful review of the patient's records and discussion with the patient and, sometimes, the parent. For adults who were treated as children and may know very little about their cancer history, this process gives them important information.

FOR PEDIATRICIANS CARING FOR A CHILD WHO IS BEING TREATED OR HAS FINISHED TREATMENT FOR CANCER

As the pediatrician, the information you receive from a child's oncology team will include recommendations for ongoing routine care, such as a re-immunization schedule and management of fevers; a treatment summary; and guidance on surveillance for disease recurrence. This communication can help specify the respective roles for the pediatrician and the oncologist, which will differ from patient to patient based on the treatments received. A child who received hematopoietic stem cell transplants or is otherwise immunosuppressed, for instance, may need to see the oncologist for routine symptoms for an extended period of time versus a patient who received less intensive therapy.

Between 3 and 5 years following completion of therapy, survivors often have a follow-up visit with their oncologist that focuses less on disease recurrence and more on organ toxicity from treatment, assessment of growth and development in the face of prior therapy, and treatment-related risks that should be evaluated. At that visit, a new survivorship care plan can be created to lay out which survivorship screenings should be conducted and when, and which subspecialists should be included in the child's care going forward.

Transition Is Often a Time of Anxiety for Children and Families

When a child finishes cancer therapy, it is often cause for both celebration and anxiety for the family. Parents may be particularly anxious about the end of therapy, the knowledge that their child will not be seen as frequently in the oncology setting, and the risk of cancer recurrence. If you have concerns about an increase in anxiety around this time, the oncology psychosocial provider at your patient's cancer center can work with you to arrange for your patient and his/her family to be seen by a community provider.

Keep Watch for Signs of Early and Late Treatment Effects, and Be Aware of Screening Recommendations

Issues around treatment-related toxicities can emerge both during treatment and shortly after transition. For instance, patients who received platinum-containing drugs might experience hearing loss. Effects of treatment that can develop in the pediatric years also include heart disease in survivors treated with anthracycline compounds and neurocognitive and neuroendocrine dysfunction in patients who received radiation for a brain tumor. A child who received radiation to the brain might have difficulties with cognition that affect school performance. If problems arise, consider referring her for neurocognitive testing. Similarly, signs of growth delay, hypothyroidism, or early or late puberty could be a sign of treatment-related endocrine dysfunction that warrants referral to an endocrinologist. The Children's Oncology Group provides detailed, peer-reviewed guidelines[4] for screening and treating survivors of pediatric cancer.

FOR INTERNISTS CARING FOR ADULT SURVIVORS OF CHILDHOOD CANCER

The Use of Radiation to Treat Childhood Cancer Is Associated With Significant Morbidities in Adulthood

Between two-thirds and three-quarters of children treated between 1970 and 1990 received radiation. In addition to the risk of radiation-induced secondary cancers, radiation also increases a patient's risk of chronic disease. For instance,

- patients who received chest radiation may develop pulmonary fibrosis, heart valve disease, or early coronary artery disease;
- patients who received brain radiation during childhood may have chronic issues with learning, vocational success, and organizational skills, as well as neuro-endocrine dysfunction;
- patients who received neck radiation have a higher risk of thyroid failure; and
- female patients who received radiation to the pelvis are at risk for ovarian failure, as well as pregnancy complications, should they become pregnant.

Recommendations on how to monitor patients for these risks vary based on the site of radiation. Patients who received neck radiation, for example, should be screened for hypothyroidism, and those who received abdominal radiation should be screened early for colon cancer (see peer-reviewed guidelines[4]).

Two Commonly Used Classes of Chemotherapy Drugs, Anthracyclines and Alkylators, Are Associated with Serious Late Effects

Anthracyclines (eg, doxorubicin, daunorubicin, and epirubicin) and alkylating agents (eg, cyclophosphamide, melphalan, and procarbazine) have been linked respectively to late-onset heart disease and infertility. When administered to adults in high doses, doxorubicin, the most commonly used anthracycline, carries a well-known risk of acute congestive heart failure (CHF). In children, however, high doses of doxorubicin can lead to asymptomatic left ventricular dysfunction many years after exposure and is associated with progression to heart failure. Pharmacologic intervention with beta-blockers and/or ACE inhibitors at early signs of asymptomatic left ventricular dysfunction may delay the onset of overt CHF, which makes it important to implement a cardiac screening plan for these patients.

Alkylating agents have been linked to low or no sperm count in men, and early menopause or primary ovarian failure in women. Encourage male patients, who are ready to become fathers, to obtain a semen analysis and, if indicated, explore assisted reproductive technology. Female patients should see a fertility specialist if they have not conceived within 6 months of starting to try to get pregnant, and those young women who are not ready to be mothers but are at risk for premature ovarian failure might consider freezing ovarian tissue, eggs, or embryos.

FOR OB-GYNS CARING FOR ADULT WOMEN WHO HAD CHILDHOOD CANCERS

Women Treated With High-Dose Alkylating Agents Are at Risk of Primary Ovarian Failure, Early Menopause, and/or Infertility

Women at risk for early menopause, who were previously exposed to alkylating agents, may be menstruating regularly; however, taking into consideration their risk for early menopause will contribute to their management, both in counseling regarding timing of pregnancy and in consideration of egg preservation. Research that my colleagues and I published in *Lancet Oncology*[5] found that many survivors of childhood cancer who eventually became pregnant took longer to conceive than other women of the same age, supporting the concept that menstruating survivors may have ovarian damage. Survivors of childhood cancer should be referred to a fertility specialist after no more than 6 months of trying unsuccessfully to get pregnant. Earlier referral is indicated when the patient has a history of pelvic radiation or high cumulative doses of alkylating agents.

Female Survivors Are at Risk of Cardiotoxicity if Their Treatment Included Anthracyclines

This risk may increase during pregnancy. Risk factors for late CHF include a history of CHF during cancer treatment, young age at exposure, radiation to the chest, and total dose of anthracyclines. Exposure to anthracyclines has been associated with development of CHF during pregnancy or in the peri-partum period. Consideration of heart disease risk based on exposure might include administering an echocardiography prior to pregnancy, as well as evaluation by a cardiologist or in a high-risk obstetric practice with expertise in cancer patients and survivors.

Women With a History of Chest Radiation in Childhood or Early Adolescence Are at Very High Risk of Developing Breast Cancer, Similar to the Risk Seen in BRCA1 and BRCA2 Carriers

These patients should start mammography and breast MRI screening at age 25 years, or 8 years after exposure, whichever is later. An ongoing study is looking at tamoxifen to prevent radiation-induced breast cancer,[6] but this is not yet standard-of-care. Because the risk is so high, consultation with a breast cancer prevention program might be warranted.

Women Who Were Treated for Childhood Cancer May Have Had Poor Bone Mineralization During Adolescence

Reasons for this might include inadequate calcium intake, insufficient estrogen production, and lack of exercise and sun exposure during their illness. They may be at risk for osteopenia and osteoporosis even if they are menstruating or receiving estrogen-replacement therapy. These patients should have an early assessment of bone health.

Whether you are an internist, pediatrician, or OB-GYN, you should provide patients who are survivors of childhood cancer with the same advice about healthy living that you urge for all your patients: do not smoke, eat healthy, and exercise. My pediatric colleagues and I are constantly seeking ways to reduce the toxicity of treatment while maintaining or improving cure rates. However, the day has not yet arrived when surviving childhood cancer is consequence-free. Together we can work to ensure our patients live as long and as healthily as possible. **EBO**

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LIVESTRONG Fertility Training: Addressing the Needs of AYA Cancer Survivors
(CONTINUED FROM COVER)

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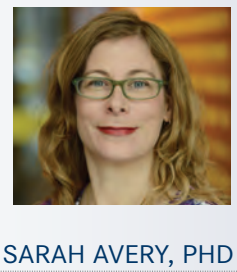

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formed decision related to their fertility and reproductive options, which is associated with increased distress levels in this group. Increased distress levels can affect cancer survivors' long-term QOL by causing unresolved grief and depression, as well as reduced life satisfaction and increased anxiety.[7]

MOST FREQUENT BARRIERS TO FERTILITY PRESERVATION

The disclosure of the risk of iatrogenic infertility, as well as information and referral to fertility preservation services, is often possible for patients prior to, during, and after treatment for cancer.[8,9] Although technologies for fertility preservation and reproduction continue to evolve—providing options today that simply did not exist for patients with cancer even a few years ago—significant barriers can prevent patients from receiving this information and the services.[9,10] Sometimes doctors fail to disclose the risks of infertility associated with treatment or they fail to refer patients to fertility preservation services; consequently, patients do not seek fertility preservation information or services prior to treatment.[11] In addition, due to the urgent need for care, there is often a very short window of opportunity to preserve fertility prior to beginning treatment. Cost is another significant barrier, as fertility preservation is generally not covered by insurance and costs average $8000 for women and $1500 for men to conduct any single fertility preservation procedure. These costs do not include the cost of pre-cycle stimulation medication for women, an average cost of $4500, or annual storage of gametes, which can cost up to $500 a year.[9]

SUPPORT FROM NATIONAL ORGANIZATIONS

Addressing fertility concerns has emerged as a major component of cancer care. Numerous organizations have created national standards that express the importance of educating all patients in their reproductive years about the impact of cancer and its treatment on their fertility, including the American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network, and the American Society of Reproductive Medicine. In 2006, ASCO issued guidelines outlining the role of oncology healthcare providers in educating their patients about fertility risks and preservation options prior to cancer treatment; the guidelines were updated in 2013.[8,12]

ASCO's guidelines call for oncologists to "address the possibility of infertility with patients treated during their reproductive years and be prepared to discuss possible fertility preservation options or refer appropriate and interested patients to reproductive specialists."[8] Despite these guidelines, research continues to indicate that providers are not routinely offering fertility information and referrals to their patients.[13,14] A 2011 study found a substantial majority of National Cancer Institute-designated Comprehensive Cancer Centers had no formal procedures to address fertility preservation, nor were they following ASCO's fertility guidelines.[15] Although ASCO's Quality Oncology Practice Initiative standards offer recommendations on documentation of fertility discussion, researchers have demonstrated that less than 70% of providers document discussions about cancer-related fertility risks and referrals to a specialist. The study results also indicated that providers are less likely to have these discussions with some minority populations and women.[11,13]

Studies have also shown that there are many barriers to healthcare providers successfully implementing the guidelines, including lack of information about the latest preservation options and communication challenges when engaging in discussions about an often sensitive topic.[10] A qualitative study by Knapp and Quinn revealed that in addition to educational barriers, healthcare providers report institutional barriers are a significant hindrance to successfully disclosing risk to patients and making referrals for preservation. For example, despite national guidelines, hospital-level policies do not exist at some institutions regarding fertility guidelines for cancer patients. In addition, healthcare providers cite an extensive case load and the short time available for appointments as barriers to disclosing this information during a visit.[10] Healthcare providers require accurate information and support tools to help explain the risk of iatrogenic infertility, fertility preservation procedures, and referral sources in order to effectively educate patients.

AN ONLINE TOOL FOR HEALTHCARE PROVIDERS

In 2014, the LIVE**STRONG** Foundation developed an online training program for healthcare professionals to address this need.[16] LIVE**STRONG** Fertility Training for Healthcare Professionals is an interactive online training course designed to engage healthcare professionals as they learn to communicate with patients about fertility risks and family-building options as a result of a cancer diagnosis and its treatment. Additionally, the course provides tools and resources for organizations to establish a systematic approach to fertility at an institutional level.

Since the launch of LIVE**STRONG** Fertility Training for Healthcare Professionals in January 2015, more than 300 individuals have registered for the training. Most of the registrants identified as a nurse or a nurse practitioner (53%). Most participants (91%) who have responded to the post-training survey have found the training helpful in their work with their patients and indicated that they are more confident in their ability to know how to discuss fertility risks related to a cancer diagnosis or cancer treatment with their patients.

In addition to fulfilling clinical quality standards, healthcare professionals have a moral imperative to provide patient-centered care that includes addressing cancer-related fertility needs. Numerous studies have captured the information and systemic challenges that physicians and institutions face when implementing the ASCO guidelines on cancer and fertility. The LIVE**STRONG** Fertility Training course was designed to address these issues. Further research on the outcomes of the LIVE**STRONG** Fertility Training will help administrators and healthcare educators better understand the effectiveness of online training tools in being a catalyst for practice change among healthcare professionals of AYAs. **EBO**

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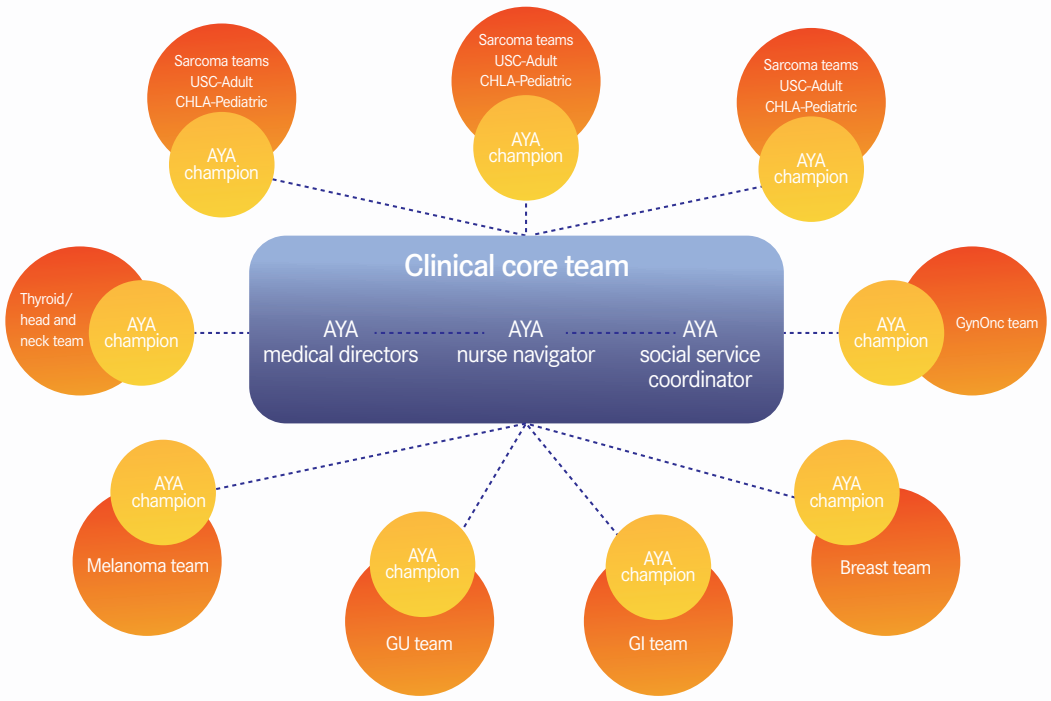
FIGURE 1. Program Model With Central AYA Team Connected to Disease-Specific Areas With Champions



AYA indicates adolescent and young adult; CHLA, Children's Hospital Los Angeles; GI, gastrointestinal; GU, genitourinary; GynOnc, Gynecologic oncology; USC, University of Southern California.

Problems that care providers face, including a lack of multidisciplinary teams, limited availability of therapeutic clinical trials focused on the AYA population, and even a lower rate of drug and device approvals for the less common cancer types seen in AYA patients can all lead to more suboptimal treatment planning. Consequently, AYA patients have been treated based on guidelines and recommendations developed exclusively for pediatric or adult oncology patients with cancer, without any regard for differences in host tolerance to treatments, tumor biology, and psychosocial developmental stage.[6-9] The unaddressed needs of this population can result in increased likelihood of misdiagnosis, late stage diagnosis, and reduced adherence to treatment and follow-up.[4,6,10]

In an effort to mitigate these gaps in care and to develop a national agenda for AYA oncology, the National Cancer Institute, in collaboration with the LIVESTRONG Young Adult Alliance, established the Adolescent and Young Adult Oncology Progress Review Group (PRG). The PRG outlined 5 imperatives for improving the outcomes of AYA patients with cancer, one of which includes a recommendation to ensure excellence in service delivery across the cancer control continuum.[11] Further, the National Comprehensive Cancer Network (NCCN) AYA Guidelines Panel strongly advises that AYA patients be referred to cancer centers with expertise and experience in treating patients in this age group and the cancers that affect them. There is a definite need for comprehensive models of cancer care that have this population's diverse needs in mind.[1,11-16]

Through the systematic and proactive provision of age-appropriate support services and a multidisciplinary approach to clinical care, the Adolescent and Young Adult Cancer Program at the University of Southern California (AYA@USC) has developed a care model to bridge the gaps experienced by this population.

MODEL AND INTERVENTION

From its inception, the care model has been sponsored by the USC Norris Comprehensive Cancer Center and structured with joint pediatric and medical oncology leadership spanning 2 major USC-affiliated academic medical centers: the Norris Cancer Hospital at the Keck Medical Center (USC) and Children's Hospital Los Angeles (CHLA). Both are private nonprofit medical institutions.

The AYA@USC clinical team works collaboratively with existing disease-specific oncology teams to bring the AYA perspective to patient care, focusing on the unique needs of this population such as fertility and psychosocial concerns. The team, comprised of 2 medical directors (pediatric oncologist and adult oncologist), a program manager, 3 part-time nurse navigators (NNs), and a social worker (SW), have streamlined resource utilization through the development of efficient algorithms within the USC and CHLA community networks. This algorithmic model of care ensures that protocol-defined patients are appropriately assessed by both nursing and social work disciplines as they assist patients with gaining access to needed services, referrals, follow-up care, and provide education uniquely tailored to AYAs. Each disease-specific oncology team identifies an AYA "champion" and provides feedback to AYA@USC.

During the nascent stages of program development, stakeholders across the healthcare spectrum were engaged in a collaborative forum in which principles were developed to ensure the successful implementation of the program. These principles include:

1. A resource or space-efficient decentralized care model in which disease-based treating oncologists continue to manage patient care.
2. AYA clinical team provides supportive care planning and recommendations.
3. AYA physician champions serve in each specialty area to align their group's AYA practice and processes.
4. Fluid and collaborative communication between the AYA clinical team and treating oncology teams.
5. Multidisciplinary and collaborative approach to program development with input from all partnering stakeholders (**FIGURE 1**).

Based on these guiding principles, program enrollment began in November 2013 and several hundred AYA patients have since been referred to the program. An overview of the clinical care and services provided to patients can be found below and in **FIGURE 2**.

1. Oncology patients (15 to 39 years old) are either referred by healthcare professionals or identified from an electronic medical record. The NN and/or SW seek permission from the treating oncology team prior to providing AYA services.
2. The NN aims to contact the patient within 1 to 2 working days to provide fertility preservation education consistent with guidelines by the American Society of Clinical Oncology and acts as a conduit to perform a preliminary evaluation with referrals.[17] See **FIGURE 3** for the fertility education algorithm.
3. The SW conducts an in-depth psychosocial assessment within 10 days, including the Distress Screening Tool and Thermometer (DT), adjusted for the AYA population. If a patient

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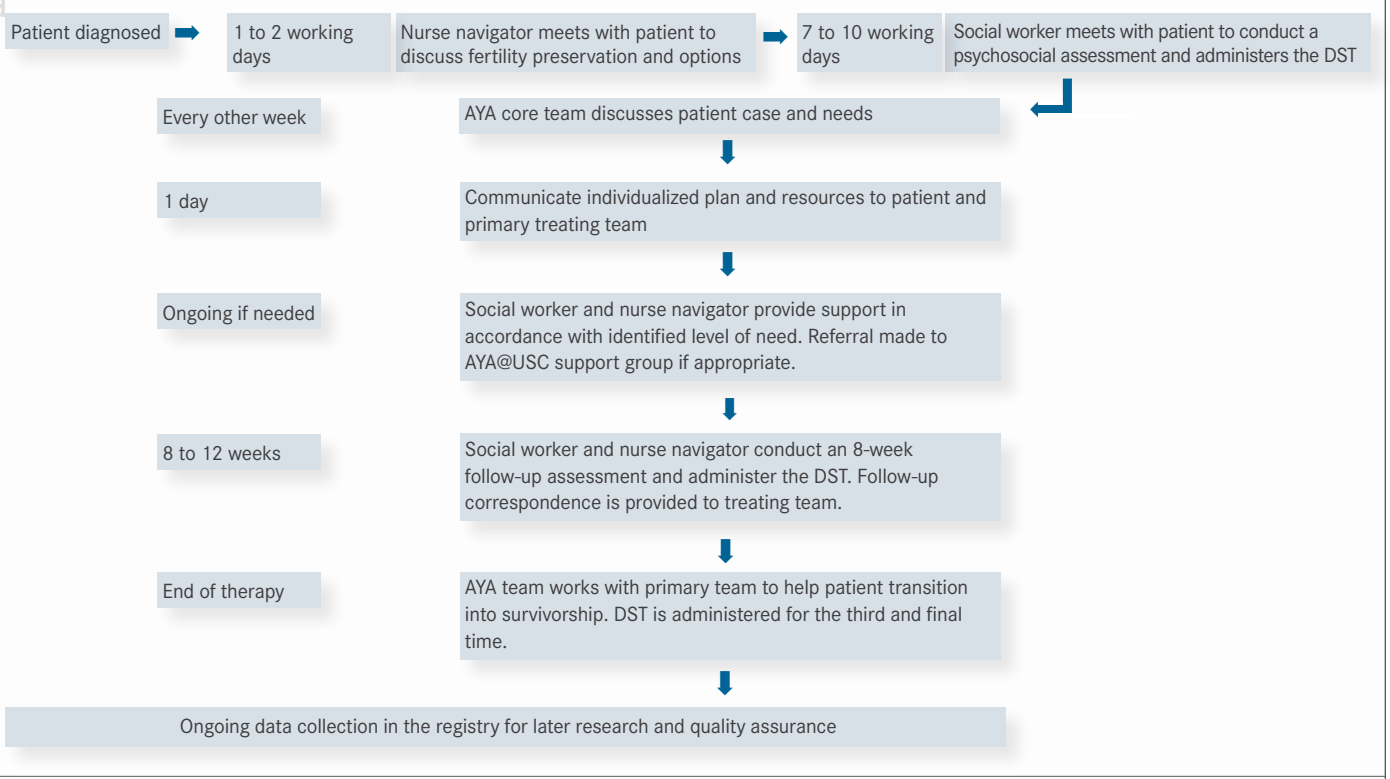
FIGURE 2. AYA@USC Oncology Care Model



AYA indicates adolescent and young adult; AYA@USC, Adolescent and Young Adult Cancer Program at the University of Southern California; DST, distress screening tool.

scores ≥7 on DT, immediate SW intervention occurs.[18,19]

4. Information gathered from the initial NN and SW assessments are presented at a bimonthly AYA team case conference; identified needs are addressed, and resources and referrals are made. Recommendations are communicated to the treating oncology team and the patient.
5. Referral to AYA@USC or regional support group is made if appropriate.
6. About 8 to 12 weeks later, an additional assessment is conducted to follow up on previously identified concerns and assessments for new issues. The DT is administered again and addressed accordingly.
7. The NN and SW contact the patient once active treatment has been completed to provide resources, education, and support while transitioning into survivorship. The DT is administered and addressed for the third time.
8. Biweekly AYA team meetings are held to discuss key findings of referred patients, challenging cases, controversies, and new evidence-based literature and developments.

Case Example 1

Patient is a 32-year-old female, diagnosed with a gastrointestinal stromal tumor; status is post complete resection. Patient rated her initial distress at 8 on a scale of 1 through 10, and her top concerns were fertility, living arrangements, finances, family dynamics, relationship status, isolation, anxiety, insomnia, and diarrhea. At initial encounter, the treatment plan was still being formulated, and it was unknown if fertility-harming therapy would be prescribed. NN provided fertility preservation education and addressed her fertility concerns. Because the patient strongly desired future biological children, she came to the decision to pursue fertility preservation prior to the start of additional therapy in order to safeguard the possibility of having a biological offspring. Referral to a reproductive endocrinologist was arranged, and the patient successfully cryopreserved oocytes prior to the start of adjuvant therapy with imatinib (Gleevec). SW addressed the practical, familial, and emotional concerns by connecting the patient with AYA resources and providing 8 individualized, brief therapy sessions to address relationship stressors. NN addressed the insomnia and diarrhea concerns by suggesting a variety of nursing interventions.

At the 8-week follow-up, the patient's distress fell to a 3 with self-reported decreased anxiety and increased family engagement. Patient utilized various resources in the community including meditation or yoga and connected with another survivor through Imerman Angels, a national nonprofit that provides peer support to cancer patients. The patient is still in active treatment, and AYA@USC will help bridge the transition into survivorship when treatment is completed.

Case Example 2

Patient is a 31-year-old male, diagnosed with sarcoma that presented with a 2-month history of increasing abdominal girth, pelvic pain, and malaise. CT scan revealed a retroperitoneal mass with metastasis to lymph nodes and lungs. Patient received 6 cycles of standard of care chemotherapy followed by surgical resection.

Patient expressed interest in having future biological children and was counseled on fertility preservation by the NN who then made arrangements for sperm banking while the patient was hospitalized. However, the patient was unsuccessful at obtaining a sperm sample due to the impact of disease on ejaculatory function.

The patient rated his initial distress at 8, citing career, finances, emotional distress, exercise ability, sexual concerns, and nutrition as top issues. He was provided with financial assistance applications, career resources, AYA-specific support resources, and individualized social work support. Through education and provision of resources, the NN addressed concerns with erectile dysfunction and decreased libido; the patient declined urological consult. AYA@USC was able to assist with referrals to occupational and physical therapies to address his exercise concerns. Referral to a nutritionist was completed.

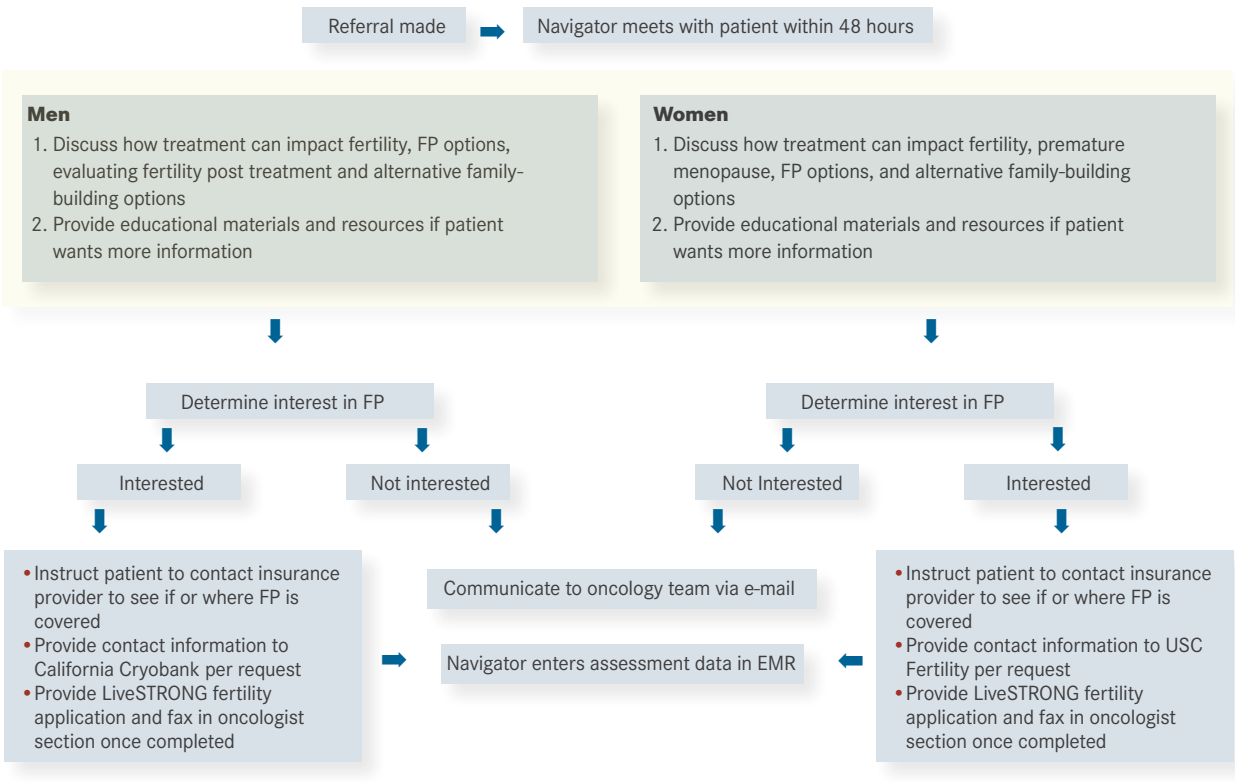
Eight weeks later, the patient rated his distress at 5. While the patient's financial concerns remained, he had not pursued any of the financial resources previously provided. Patient verbalized new concerns surrounding his social life and, per AYA recommendation, began participating in the AYA@USC patient support group. Emotional concerns persisted and individualized social work support was utilized again. Occupational and physical therapy were continued to address the patient's persistent concern with his ability to exercise.

The patient is currently pursuing surgical intervention for additional treatment. AYA@USC will continue to follow him and eventually will bridge the transition into survivorship.

DISCUSSION

AYAs with cancer have not benefited comparably from the increased survival and reduced mortality experienced by both older and younger cancer patients.[1] Tremendous gaps concerning how best to treat AYA patients with cancer exist while supportive care services, when available, can often be fractured and uncoordinated. In general, without a coordinated AYA program, patients who already experi-

FIGURE 3. Fertility Preservation Patient Education Algorithm



EMR indicates electronic medical record; FP, fertility preservation.

ence lower levels of insurance coverage and healthcare access further experience referral issues, problems with copay and negotiation of covered services, and lack of specialized services such as fertility preservation.[20-23] Additionally, in the academic medical system setting, available clinical trials are typically targeted to either the pediatric or adult end of the age spectrum—AYA@USC was conceived in response to these gaps.

Downstream benefits of the AYA program include the impact on health limitations experienced by survivors. Kirchhoff et al highlight how AYA survivors are not receiving primary medical care services and report cost barriers to care at levels beyond these general age differences. Hidden costs related to prolonged economic loss of productivity, transportation issues for patients getting to treatment and follow-up appointments, and fluctuations in caregiver or childcare services can compound and present barriers associated with healthcare for AYAs.[20,22,24,25] The AYA@USC clinical team serves as a bridge to AYA survivorship services when treatment is completed. In the LIFE Cancer Survivorship & Transition Program at USC, detection and management of late effects, assessment of psychosocial functioning, health-related education, and financial and employment challenges are all addressed to improve outcomes for AYA survivors.[26]

CONCLUSION

The AYA@USC program was developed to ensure excellence in care across the cancer control continuum for AYAs. Programmatic development was guided by recommendations outlined in the PRG report to adopt AYA patient-centered approaches to care, in collaboration with the NCCN clinical practice guidelines in AYA oncology.[11,16] Sustaining these standards of cancer care for AYAs has required the ongoing communication and commitment of a diverse array of stakeholders.

Future plans for the program include the analysis of clinical data (distress levels, fertility consults, and pain scores), financial data (length of stay, inpatient readmission rates, and health-related quality of life), and patient and staff satisfaction surveys to inform future interventions and best practices. The AYA@USC model was designed to be exportable to other facilities including Los Angeles County Hospital+USC—the largest single provider of healthcare in the county—to build a regional network for AYA patient care. The hope is models such as these will contribute to the impending national standard of care for AYAs with cancer. **EBO**

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