of G-CSFs in oncologic therapy and their role in the prophylaxis and treatment of FN. By adhering to evidence-based clinical guidelines, healthcare providers have the potential to provide optimized treatment regimens and lower the risk of FN for their patients.

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The Value of Granulocyte Colony-Stimulating Factors in Managing Febrile Neutropenia

Cost Burdens of Cancer and Febrile Neutropenia

In 1987, the total medical cost of cancer in the United States, adjusted to 2007 US dollars, was $24.7 billion. From 1987 to the period between 2001 and 2005, costs nearly doubled, to approximately $48.1 billion.[1] However, despite significantly increased spending on oncologic treatment, survival rates have not improved proportionally. As much as an estimated 30% of healthcare expenditures provide minimal value in changing patient outcomes. Despite the United States investing more healthcare dollars than other countries, the life expectancies of men and women in the United States are shorter than those in comparable industrialized nations.[2]

In 2013, the estimated cost of febrile neutropenia (FN) in the United States ranged from $16,054 to $34,756 per patient, the highest in the world (followed by Singapore, Europe, Australia, Canada, and Spain); the per-patient cost outside the United States ranged from $5819 to $13,823.[3] To contain and manage rising costs associated with febrile neutropenia (FN), it is important to make value-based assessments before administering treatment.

TABLE. FDA-Approved Targeted Therapies for Colon Cancer[7-10]

TREATMENT AGENT	INDICATION
Neupogen (filgrastim)	• Decrease the incidence of infection, as manifested by febrile neutropenia (FN), in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a significant incidence of severe neutropenia with fever • Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML) • Reduce the duration of neutropenia and neutropenia-related clinical sequelae, eg, FN in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT) • Mobilize hematopoietic progenitor stem cells into peripheral blood for collection by leukapheresis • Reduce the incidence and duration of sequelae of severe neutropenia (eg, fever, infection, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia • Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome; H-ARS)
Neulasta (pegfilgrastim)	• Decrease the incidence of infection, as manifested by FN, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of FN • Increase survival in patients acutely exposed to myelosuppressive doses of radiation (H-ARS)
Granix (tbo-filgrastim)	• Reduction in the duration of severe neutropenia in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of FN
Zarxio (filgrastim-sndz)	• Decrease the incidence of infection, as manifested by FN, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a significant incidence of severe neutropenia with fever • Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with AML • Reduce the duration of neutropenia and neutropenia-related clinical sequelae, eg, FN in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by BMT • Mobilize autologous hematopoietic progenitor stem cells into peripheral blood for collection by leukapheresis • Reduce the incidence and duration of sequelae of severe neutropenia (eg, fever, infection, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia or idiopathic neutropenia

Granulocyte Colony-Stimulating Factor Value in Primary Prophylaxis

When granulocyte colony-stimulating factors (G-CSFs) are used for primary prophylaxis, which refers to their use in the time period after the first cycle of a cancer patient's chemotherapy but before the development of neutropenia, they reduce the risk, severity, and duration of FN. Even though G-CSFs increase the cost of cancer care, they significantly reduce complications such as expensive hospitalization, morbidity, and mortality.[2] Costs associated with FN include direct costs such as inpatient management, antibiotics use, and duration of hospital stay, as well as indirect costs such as the loss of caregiver and patient productivity.[3]

Recent economic analyses suggest that if the risk of FN is approximately 17% to 20%, then G-CSFs may become a cost-saving therapy. The cost savings associated with the use of G-CSFs come primarily from reducing expensive inpatient hospitalizations, with recent median estimates of FN hospitalizations ranging from $2000 to $3000 per day.[2,4] A single hospital admission for febrile neutropenia results in average costs of $22,000 or more.

However, the substantial costs associated with G-CSFs become a limiting factor in administering them for prophylaxis. G-CSFs are among the many components contributing to significant costs of cancer-related healthcare.[2] The results of a study evaluating the value of G-CSF prophylaxis in women with ovarian cancer undergoing chemotherapy »

indicated that cost-effectiveness heavily relied on the patient's individual risk of FN. Patients with a low risk (approximately 5%) of developing FN needed an estimated $47,000 of G-CSF prophylaxis to prevent a single hospitalization. On the other hand, G-CSF prophylaxis in patients with a risk of 17% to 20% of developing febrile neutropenia was considered to be a cost-saving strategy.[2]

Challenges in Defining G-CSF Value

Defining and determining G-CSF value, or outcomes divided by costs, is a difficult challenge. In other parts of the world or within the United States itself, treatment costs may vary by region. Though the duration of a patient's life may be an outcome measure, it increases the complexity of determining value because living longer leads to patients incurring more costs, collecting Social Security, and using resources, among many other factors. Other variables taken into consideration when defining outcomes include duration of life, quality of life, health status, adverse outcomes, and opportunities to receive care. Additionally, it is difficult to assess the value of G-CSFs for supportive care because the potential impacts of other supportive care measures, such as prophylactic antibiotics or myeloid growth factors, are often poorly documented in clinical trials. Furthermore, in clinical practice, evidence suggests that G-CSFs may be underused in high-risk patients and overused in low-risk patients.[2]

Evaluating costs may be equally challenging. The various costs that must be considered include direct medical expenditures, work loss, caretaker burden, transportation, and medical support devices. These factors complicate understanding the cost versus benefit of G-CSFs and prompt the need for a uniform definition of value. In a recent review article published in the *Journal of the National Comprehensive Cancer Network*, Dinan and colleagues suggested that the oncology community should create a common definition of valuable cancer care to implement evidence-based guidelines and policies.[2]

Understanding G-CSF Value Through the Societal Perspective

Various definitions of outcomes from patients, physicians, payers, policy makers, manufacturers, and society add to the complexity of understanding G-CSF value. For example, payers may focus on containing costs, while physicians and patients may focus on improving outcomes.[2] When trying to determine the value of treatment, understanding the societal perspective may be the most appropriate approach because it prevents underestimating costs of any given stakeholder.[3]

Because the societal perspective is the most comprehensive approach to understanding value, researchers designed a 2014 study to assess the societal value of administering G-CSFs, compared with the costs associated with not administering G-CSFs.[6] In this study, Vanderpuye-Orgle and colleagues assessed clinical and nonclinical outcomes. Clinical outcomes from G-CSF treatment included savings from reductions in FN hospitalizations, reductions in antibiotic usage, and reductions in morbidity due to the ability to administer high-dose chemotherapy. Nonclinical outcomes from G-CSF treatment included savings from reducing indirect costs, such as loss of productivity and diminished quality of life. The total clinical value of G-CSFs was an estimated $8.24 billion, with the most value generated by increased chemotherapy intensity; this accounted for 59.83% of the clinical value. The total nonclinical value of G-CSFs was an estimated $2.3 million, with the most nonclinical value (99%) generated by avoiding indirect costs. Overall, the total societal value of G-CSFs was $8.5 billion.

Because G-CSF manufacturers are a part of society, it is important to take their perspective into account. Manufacturers generated a value of $1.306 billion in profits from producing and selling G-CSF products. The combined value, which is the sum of the total societal value and manufacturer's profits, was $9.806 billion. Out of the total benefits gained from G-CSFs, manufacturers accounted for 15.4% of benefited value and the rest of society, which consists of mainly patients, accounted for 84.6% of benefited value.[6]

As noted in **Table**,[7-10] filgrastim and pegfilgrastim have been approved with indications for treating FN. In 2011, the combined US sales of filgrastim and pegfilgrastim reached $5.2 billion,[2,6] while they helped avoid $8.5 billion of clinical and nonclinical costs. Therefore, the agents promoted overall healthcare savings. When comparing filgastrim and pegfilgastrim for FN prophylaxis post chemotherapy, no clinically significant difference exists between the 2 agents in reducing the duration of severe FN in patients with acute myeloid leukemia.[11]

Conclusion

FN imposes a great economic burden on various stakeholders, who are concerned by different types of costs. Because the value in treating oncology patients varies depending on the perspective of an individual, it is important to consider the impact of G-CSFs on society. Two components of value include clinical and nonclinical value. Even though 2 major products on the market cost $5.2 billion combined, they helped save society $8.5 billion. The conclusion is that there is value in administering G-CSFs.

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Guidelines in the Management of Febrile Neutropenia for Clinical Practice

Febrile neutropenia (FN) is a serious complication of cancer chemotherapy that can lead to delays in treatment and necessary dose reductions of chemotherapy, which compromise treatment efficacy. Approximately 1% of patients with cancer receiving chemotherapy develop FN, which contributes to morbidity and mortality, and imposes substantial burdens on healthcare resource use for management of this affected population.[1]

Neutropenia is characterized by a reduction in neutrophils below normal counts, usually occurring within 7 to 12 days following cancer chemotherapy.[2] It is diagnosed with a blood test that confirms an absolute neutrophil count (ANC) of less than 500 cells per microliter following cytotoxic chemotherapy, or by an ANC expected to decrease to less than 500 cells per microliter within 48 hours. Due to reduced levels of neutrophils in circulation, patients with neutropenia may have an impaired ability to fight infections.[3] Hence, even a minor infection for patients with neutropenia may become very serious. It is crucial to monitor patients for signs and symptoms of infection, which may present as fever, chills, or sweats. Other signs and symptoms of infection for patients with FN are provided in **Table 1**.[2]

Neutropenia may be accompanied by fever originating from an underlying infection. Fever may be the sole indicator of an underlying infection in patients with chemotherapy-induced neutropenia; other signs and symptoms of inflammation may be absent.[4] Patients with neutropenia thus must be assessed for risk of severe infection immediately at presentation of fever. FN is defined by an oral temperature greater than 101ºF from a single reading or an oral temperature of at least 100.4ºF sustained over a 1-hour period or reported from 2 consecutive readings in a 2-hour period.[1,4]

Initial Physical Assessments

Patients presenting with FN undergo initial physical assessments for potential infection. The patient's risk of developing an infection-related complication must be determined so that appropriate early management can begin. Because patients with FN may have minimal or absent symptoms of bacterial infections, detection requires close examination of the most commonly infected sites. Patients with FN are initially investigated for infection on sites of previous procedures or catheters, as well as on or in the skin, alimentary tract, oropharynx, gastrointestinal tract, lungs, genitourinary region, and respiratory system. Chest radiography may be indicated if there are any signs and symptoms of respiratory infection; this is to rule out pneumonia, which can progress rapidly in patients with FN.[4,5] »