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Fixed-Duration Therapy With Carfilzomib-Cyclophosphamide-Dexamethasone May Lead to Improved Responses Compared With Bortezomib-Cyclophosphamide-Dexamethasone at First Myeloma Relapse

Lynne Lederman, PhD

KWEE YONG, MD, PHD, presented the results of the Myeloma United Kingdom (MUK) *five* phase 2 study that compared carfilzomib plus cyclophosphamide and dexamethasone (KCd) with bortezomib plus cyclophosphamide and dexamethasone (VCd) in patients with multiple myeloma at first relapse or with primary refractory myeloma.[1]

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Beat AML Trial Proves Feasibility of Rapid Treatment Assignment Following Diagnosis

Kristie L. Kahl

HEMATOLOGISTS MAY HAVE THE ability to determine acute myeloid leukemia (AML) subtype based on genetic analysis of blood samples in 7 days or less, a process that could soon be an integral part of diagnosing and treating this patient population, according to Amy Burd, PhD.

Initial findings from the Beat AML study showed that rapid genetic testing in patients with AML was feasible and helpful, and that a

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Fixed-Duration Therapy With Carfilzomib-Cyclophosphamide-Dexamethasone May Lead to Improved Responses Compared With Bortezomib-Cyclophosphamide-Dexamethasone at First Myeloma Relapse

(continued from cover)

One study that may inform the choice of proteasome inhibitor to be used at first relapse is ENDEAVOR, which compared carfilzomib plus dexamethasone with bortezomib plus dexamethasone in a doublet for extended therapy in relapsed myeloma. According to Yong, of University College London Hospitals NHS [National Health Service] Foundation Trusts, in the United Kingdom, triplet regimens are a standard of care. The MUK *five* phase 2 study was designed to assess the antimyeloma activity of carfilzomib versus bortezomib in triplet regimens with cyclophosphamide plus dexamethasone in the second line only. The second-line patient population was selected from the subset analysis of the ENDEAVOR trial; the patients who received 1 prior line of therapy appeared to derive a significant benefit from carfilzomib compared with patients who were treated with later lines.

In part 1 of the MUK *five* study, 300 patients with multiple myeloma at first relapse or who were refractory to 1 prior line of therapy were randomly assigned 1:2 to VCd (n = 99) or KCd (n = 201). Patients received eight 21-day cycles of subcutaneous bortezomib at 1.3 mg/m^2 on days 1, 4, 8, and 11 in the VCd arm. Patients in the KCd arm received six 28-day cycles of intravenous carfilzomib at 20 mg/m^2 on days 1, 2, 8, 9, 15, and 16. In both arms, patients also received 500-mg oral doses of clophosphamide on days 1, 8, and 15, along with 40-mg oral doses of dexamethasone weekly. Patients in the KCd arm received an additional dose of dexamethasone on day 22. The decision to treat with a fixed duration was made because of the potential for neurotoxicity of long-duration therapy.

In the second part of the study, patients in the KCd arm who had achieved stable disease or better (n = 141) were then randomly assigned 1:1 to carfilzomib maintenance therapy (n = 69) or to further observation (n = 72) after 6 cycles of KCd. The study design is shown in the **Figure**, and the results were presented in a different session of the recent American Society of Hematology meeting.

The coprimary end points of the trial were the rates of very good partial response (VGPR) at 24 weeks (noninferiority of the treatments) and of progression-free survival ([PFS] superiority of carfilzomib maintenance).

To participate in the trial, patients needed to have multiple myeloma at first relapse, be refractory to 1 prior line of therapy, or have adequate organ function. Key exclusion criteria included significant comorbidity or cardiovascular disease (defined by the New York Heart Association), class III or IV heart failure, myocardial infarction within the last 6 months, uncontrolled hypertension, previous carfilzomib therapy, a disease that was previously refractory to bortezomib, or significant neuropathy within the last 14 days.

A total of 200 patients (median age, 68 years) were analyzed in the KCd group, after 1 patient was found to be ineligible after a random assignment had no baseline data. Approximately one-fifth of patients were 75 years or older, and median time from the last treatment was about 20 months. Roughly half the patients had stage II/III disease according to the International Staging System

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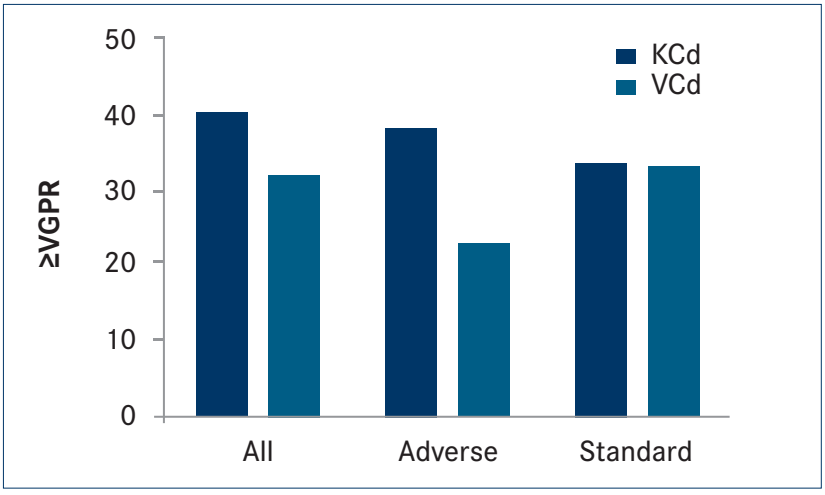
FIGURE. Study Design of MUK *five*



KCd indicates carfilzomib plus cyclophosphamide and dexamethasone; VCd, bortezomib plus cyclophosphamide; VGPR, very good partial response.

TABLE. Responses at 24 Weeks

	KCd (n = 200)	VCd (n = 99)
≥VGPR, all patients	40.2%	31.9%
≥VGPR, high-risk subgroup	38.2%	21.9%
≥VGPR, standard-risk subgroup	34.5%	33.3%
ORR (≥PR), all patients	84.0%	68.1%
ORR, high-risk subgroup	79.4%	68.9%
ORR, standard-risk subgroup	87.3%	70.4%

KCd indicates carfilzomib plus cyclophosphamide and dexamethasone; ORR, overall response rate; PR, partial response, VCd, bortezomib plus cyclophosphamide; VGPR, very good partial response.

(ISS), and two-thirds had prior autologous stem cell transplantation (ASCT). Cytogenetic information was available for 63% of patients, approximately 50% of whom had high-risk myeloma defined by at least 1 of the following: deletion 17p, gain 1q, translocation (t)(4;14), t(14;16), or t(14;20).

At the end of the first part of the study (24 weeks), more patients in the KCd arm than in the VCd arm were able to receive the maximum allocated dose. Most commonly, when patients reached the maximum number of cycles allowed, they discontinued treatment. A small number of patients also discontinued treatment due to disease progression or toxicity. Because of physician's choice or patient withdrawal, more patients discontinued VCd than KCd. Safety data were not presented.

The primary end points were met. For VGPR, KCd was noninferior to VCd; responses are summarized in the **Table**.

When the high-risk group was further divided into cytogenetic subgroups, patients with deletion 17p or adverse immunoglobulin heavy chain (IgH) rearrangement had a more "striking" benefit compared with the standard-risk group (KCd vs VCd for VGPR), according to Yong. However, she cautioned that the number of patients in each group was relatively small, and mutations were not mutually exclusive. In a subgroup analysis, both risk groups seemed to benefit equally in overall response rate (ORR) with KCd. Other groups in which KCd was favored in ORR included early relapse versus later relapse ($P = .028$) and prior ACST versus no prior ASCT ($P = .038$).

Median PFS was 11.9 months for KCd versus 10.2 months for VCD (HR, 0.95; 80% CI, 0.77-1.18). Median TTNT was not significantly different between treatment arms, with 19.1 months for KCd versus 17.1 months for VCd (HR, 0.74; 90% CI, 0.53-1.02; $P = .1176$).

Yong concluded that KCd is noninferior to VCd in terms of VGPR response and superior in terms of ORR when used at first relapse for a fixed duration therapy. In patients with high-risk genetics, KCd is superior in terms of VGPR rate; this may be driven largely by deletion 17p and adverse IgH. Importantly, deeper responses in high-risk patients in the KCd arm are not likely related to the amount of treatment received.

Yong showed Kaplan-Meier curves of PFS by treatment according to cytogenetic risk; neither treatment illustrated an advantage in either risk group. She attributed this to small numbers of patients and large confidence intervals. Approximately one-fifth of patients received bortezomib, and there did not appear to be a difference in response to KCd based on prior bortezomib use.

Yong observed that the inferior response in the KCd arm for the ENDEAVOR trial was likely related to the patient population, as they were treated at first relapse when they were not eligible for a second ASCT. According to Yong, a selection of a "less well-performing group of patients, including those with early relapse and those who are older, [are] not eligible for transplantation. This is reflected in the ISS stage, and perhaps in the high-risk genetics." ◆

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Beat AML Trial Proves Feasibility of Rapid Treatment Assignment Following Diagnosis

(continued from cover)

precision medicine approach is possible for these patients, who must be treated urgently given the disease's rapid progression.[1]

In the study, 273 patients aged 60 years or older were identified as candidates for targeted therapy within 7 days of their samples arriving at a reference lab for testing, compared with just 12 who were not. "Implementation of a rapid treatment assignment umbrella study in elderly patients with AML is feasible, with [more than] 95% of patients assigned to treatment in less than 7 days," Burd said during a press conference at the 2018 American Society of Hematology Annual Meeting, where the data were presented.

The multiarm, multisite collaborative trial, led by the Leukemia and Lymphoma Society (LLS), based in White Plains, New York, is designed to test targeted therapy approaches for improving the generally poor prognosis among patients with AML.

"Acute myeloid leukemia is the most commonly diagnosed leukemia, with 20,000 patients a year and an overall survival of [approximately] 25%," said Burd, vice president of research strategy at LLS, referring to the 5-year rate. "It is also the most lethal adult leukemia."

"We know now that AML is a heterogenous disease. It is driven by the serial acquisition of mutations that lead to interpatient heterogeneity, in both biology and clinical response," she added. "[Because of this], coupled with the increasing evidence of efficacy for targeted therapies in AML, we hypothesized: Could we improve outcomes by matching patients to the appropriate [targeted] therapy?"

In her presentation, Burd, lead author of the Beat AML study, discussed whether a multicenter clinical trial could use genetic profiling to assign patients to molecularly defined, subtype-specific therapies within 7 days. In addition, the researchers aimed to delineate the potential for new therapies to improve outcomes among older patients with AML in the frontline setting.

Objectives of Umbrella Trial

The ongoing Beat AML trial has 3 primary objectives: to determine the feasibility of completing molecular, immunophenotypic, and/or biochemical studies in 7 or fewer calendar days; to assess the feasibility of assigning patients to substudies according to a master protocol based on results from the testing; and to evaluate the clinical efficacy of novel treatment strategies in each of the substudies.

To be eligible, patients must be newly diagnosed, with no prior AML treatment other than hydroxyurea, and aged ≥60 years at the time of diagnosis. Burd noted these requirements are in line with FDA recommendations to incorporate broad eligibility criteria to capture the majority of patients with AML. The malignancy is most frequently diagnosed among people aged 65 to 74 years; median age at diagnosis is 68 years.[2]

Many patients enrolled were 75 years or older (n = 108; 37.9%) and male (58.6%). To create a genetic profile for each patient, the researchers applied 3 genetic analysis techniques: cytogenetics, polymerase chain reaction, and next-generation sequencing.

Patients were then considered for therapy using a precision medicine–based stratification algorithm that considered assignment for:

- Known responsive attributes, such as core-binding factor (CBF) AML (CBF-AML) and *NPM1* mutation–positive/*FLT3* wild-type AML
- Driver cytogenetic aberrations, such as 11q23/*MLL*-rearranged AML and *TP53* wild-type/complex karyotype AML
- A mutation clone with a variant allele frequency (VAF) ≥0.3 by next-generation sequencing[3]

If patients were not assigned to a genomic group during initial stratification, a second run-through of the algorithm was performed assessing for a mutation clone with VAF ≥0.2.

From highest to lowest, genomic stratification assignments were prioritized by CBF-AML, NPM1+/*FLT3* wild-type, 11q23/*MLL*-rearranged, *IDH2*+, *IDH1*+, *TP53*+, *TP53* wild-type/complex karyotype, *FLT3*-ITD+ or FLT3-TKD+, WT1+ or TET2+, and marker-negative AML.

Beat AML Update

The study, which launched on November 16, 2016, has enrolled 356 patients thus far; however, 66 patients were removed from the study because they turned out to not have AML upon laboratory analysis.

Of 285 patients who were identified as candidates for treatment, 146 have gone on to the second phase of the study, where they have been treated in a clinical trial for experimental therapies targeting their AML subtype.

Of those who were not treated in phase 2 (n = 139; 48.8%), most chose other therapies such as standard care (n = 57; 20%), an alternative trial after assignment (n = 26; 9.1%), palliative care (n = 23; 8.1%), or an alternative treatment

before clinical assignment (n = 20; 7%). Seven patients (2.5%) died during the 7-day period, and outcomes for 6 participants (2.1%) were considered "not specified" at the time of study analysis.

Burd emphasized that, although clinicians offered treatment assignment within 7 days, the ultimate decision was always guided by what was best for the patient, "even if that means a treatment [option] outside of the study," she added.

In 2016, the study included just 3 experimental treatment arms; today, 11 substudies of therapies developed by 7 different pharmaceutical companies are ongoing under the Beat AML umbrella. These include studies into the novel drugs entospletinib, a SYK inhibitor; pevonedistat, an Nedd8 inhibitor; and BI 836858, an anti-CD33 monoclonal antibody. The study also has open arms testing 2 FDA-approved drugs: enasidenib (Idhifa), an IDH2 inhibitor, and gilteritinib (Xospata), a FLT3 inhibitor.

"The majority of patients assigned to protocol therapy proceeded to trial, with an increase in the frequency [of trial assignment] as new protocols opened," Burd said. "And we've seen promising efficacy in several of the treatment arms to date."

Because of AML's rapid progression, and the urgent need to begin treatment as soon as possible, press conference moderator Joseph R. Mikhael, MD, chief medical officer of the International Myeloma Foundation, North Hollywood, California, applauded the efforts of the Beat AML investigators: "One of the greatest challenges we've faced in the concept of precision medicine is that, by the time you determine what is best for that patient for diseases like AML and many other hematologic diseases, in a sense, the horse is already out of the barn, meaning you have to have started the patient on treatment already or else their disease could have progressed quite rapidly."

"When we can employ the expertise of artificial intelligence, we can come up with those answers more quickly," he added. "Trying to reduce that window to 7 days [or less] is important. To be able to obtain these results early is so fundamental." ◆

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Maintenance Ixazomib Extends Progression-Free Survival in Newly Diagnosed Multiple Myeloma

Gina Columbus

TWO-YEAR MAINTENANCE THERAPY with ixazomib (Ninlaro) led to a 39% improvement in progression-free survival (PFS) compared with placebo in patients with newly diagnosed multiple myeloma who achieved a partial response (PR) to induction treatment with a proteasome inhibitor and/or an immunomodulatory (IMiD) agent following autologous stem cell transplant (ASCT), according to results of the phase 3 TOURMALINE-MM3 trial presented at the 2018 American Society of Hematology Annual Meeting.

"This is the first randomized, double-blind, placebo-controlled trial of a proteasome inhibitor for maintenance treatment after transplant," said lead study author Meletios A. Dimopoulos, MD, professor and chairman, Department of Clinical Therapeutics at the University of Athens School of Medicine in Athens, Greece, in a presentation during the conference. "Ixazomib represents a new treatment option for maintenance after transplantation."

Relapse following ASCT is nearly unavoidable in multiple myeloma, Dimopoulos said, explaining that maintenance therapy after ASCT may delay disease progression and prolong survival. Although lenalidomide (Revlimid) is approved by the FDA in the maintenance setting, he noted that 29% of patients discontinued its use due to treatment-emergent adverse events (AEs). The justification for ixazomib, therefore, is that it is given as a once-weekly oral dose and has a manageable safety profile.

Ixazomib was approved by the FDA in November 2015 for use in combination with lenalidomide and dexamethasone as a treatment for patients with multiple myeloma who have received at least 1 prior therapy.

TOURMALINE-MM3 evaluated weekly treatment with ixazomib versus placebo in newly diagnosed patients who experienced a PR to a proteasome inhibitor or IMiD as induction therapy followed by single ASCT and 200 mg/m^2 of melphalan. A total of 656 patients were randomized 3:2 to receive either ixazomib (n = 395) or placebo (n = 261) on days 1, 8, and 15 of 28-day cycles, for up to 26 cycles. After the first 4 cycles of treatment, patients increased their dose of ixazomib or placebo from 3 mg to 4 mg (n = 317 on ixazomib, n = 222 on placebo).

Treatment continued until disease progression or unacceptable toxicity. The primary end point was PFS as assessed by an independent review committee (IRC), and the key secondary end point was overall survival (OS).

To be eligible for enrollment, patients aged >18 years had a confirmed diagnosis of multiple myeloma with documented local cytogenetics/fluorescence in situ hybridization before ASCT; International Staging System (ISS) disease stage at the time of diagnosis; a documented response to ASCT; and an ECOG performance status of 0 or 2. Patients were excluded if they relapsed following or were unresponsive to front-line therapy, underwent tandem ASCT, had comorbidities or other severe conditions, or received post-ASCT consolidation therapy.

Baseline patient and disease characteristics were similar between the arms. The patients' median age was 59 years. There was an equal percentage of minimal residual disease (MRD)–negative patients in each arm (33%) and the percentage of MRD-positive patients was comparable (63% vs 61%). Fifteen patients in the ixazomib arm and 14 in the placebo arm were not evaluable.

In the ixazomib group, 15% of patients had high-risk cytogenetic features, 64% had standard-risk cytogenic features, and 21% were unclassifiable, compared with 21%, 58%, and 21% in the placebo group, respectively. Fifty-nine percent of patients in each arm had induction therapy composed of a proteasome inhibitor without an IMiD agent; 11% in each received an IMiD without a proteasome inhibitor; and 30% in each group received both agents. The most common induction regimens were bortezomib (Velcade), cyclophosphamide, and dexamethasone (46%); bortezomib, thalidomide (Thalomid), and dexamethasone (19%); and cyclophosphamide, thalidomide, and dexamethasone (5%). Thalidomide was used in 87% of patients who received an IMiD.

Patients were stratified by induction regimen, ISS disease stage, and response after transplantation. The median duration of treatment at 4 mg was 15.2 months on the ixazomib arm and 16.2 months in the placebo group.

Results showed the median PFS was 26.5 months with ixazomib compared with 21.3 months with placebo (HR, 0.72; 95% CI, 0.582-0.890; P = .002), meeting the study's primary end point.

The PFS benefit was observed across patient subgroups, including those aged between 60 and 75 years, those with high- and standard-risk cytogenetics, and patients with ISS stage III disease. In patients with MRD-negative disease, the median PFS was 38.6 months and 32.5 months with ixazomib and placebo, respectively. The median PFS was 23.1 months with ixazomib and 18.5 months with placebo in patients with MRD-positive disease. Among those who had MRD-positive disease, 12% and 7% converted to MRD-negative disease in the ixazomib and placebo arms, respectively.

At a median follow-up of 31 months, 14% of deaths had been reported and OS data are not mature; however, Dimopoulos noted that the median OS has not been reached in either arm and investigators are continuing follow-up.

Additionally, 46% of patients on the ixazomib arm had improved IRC-assessed responses, compared with 32% of those on the placebo arm. Of patients on ixazomib who had a very good partial response (VGPR) at time of study entry, 43% had that transform to a complete response (CR) after treatment, versus 32% of patients on placebo. Patients in PR at time of study entry also improved to a CR or VGPR with ixazomib (53%) versus placebo (34%).

Regarding safety, all-grade treatment-related AEs occurred in 78% of ixazomib-treated patients versus 58% of those in the placebo arm. Grade ≥3 AEs were more common with ixazomib (19%) versus placebo (5%). Overall, 7% of patients on ixazomib discontinued treatment compared with 5% of patients administered placebo, while 19% and 5% of patients on ixazomib and placebo had dose reductions, respectively. A total of 79% of patients on ixazomib versus 86% of those on placebo, who did not discontinue therapy due to disease progression, completed the full 24 months of treatment.

Dimopoulos noted that maintenance ixazomib was not associated with an increase in hepatic, cardiac, or renal AEs. Moreover, there was no difference in the rate of new primary malignancies (3% in each arm). However, AEs of any cause were more prevalent in the ixazomib arm versus placebo: nausea (39% vs 15%), diarrhea (35% vs 24%), vomiting (27% vs 11%), and arthralgia (22% vs 12%). There was 1 death in the ixazomib arm versus none in the placebo arm.

Quality of life (QoL) was also preserved with ixazomib treatment. EORTC QLQ-C30 and EORTC QLQ-MY-20 scores indicated similar patient-reported QoL in both arms over time.

Additional studies of ixazomib combinations and treatment to progression are ongoing to further improve patient outcomes, Dimopoulos concluded. ◆

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Carfilzomib Plus Lenalidomide and Dexamethasone Compares Favorably With Bortezomib Plus Lenalidomide and Dexamethasone in Observational Study in Newly Diagnosed Myeloma

Lynne Lederman, PhD

OLA LANDGREN, MD, PHD, presented results of treatment with carfilzomib plus lenalidomide and dexamethasone versus bortezomib plus lenalidomide and dexamethasone from the Clinical Outcomes in Multiple Myeloma to Personal Assessment (CoMMpass) of Genetic Profile study (NCT01454297), a prospective, longitudinal, observational study of patients with newly diagnosed multiple myeloma (NDMM).[1] Currently, the standards of care for patients with NDMM are triplet regimens incorporating a proteasome inhibitor (PI) and an immunomodulatory drug (IMiD). Combinations of carfilzomib plus lenalidomide and dexamethasone (KRd) and bortezomib plus lenalidomide and dexamethasone (VRd) are 2 options for NDMM that are included in the National Comprehensive Cancer Network guidelines in the United States, said Landgren, of Memorial Sloan Kettering Cancer Center in New York.

Trial Design

Because no data are available from randomized, controlled trials comparing the effectiveness and tolerability of KRd with that of VRd in the newly diagnosed setting, this prospective, nested, case-control study was conducted using data from the Multiple Myeloma Research Foundation CoMMpass study, enrolling patients from Multiple Myeloma Research Consortium sites. "What you are looking at here today are real-world data from investigator-sponsored trials and real-world data from standard of care," Landgren said.

The study enrolled 1143 patients with NDMM, starting in the third quarter of 2011, from 90 sites in Canada, Italy, Spain, and the United States. These patients were treated with an IMiD and/or a PI as part of their initial regimen.

Of the selected patients, 149 were treated with KRd and 460 with VRd, reflecting the fact that VRd was the preferable therapy at the time the study was initiated.

KRd patients were matched to VRd patients using propensity score matching, which included age, gender, International Staging System stage, and renal insufficiency as covariates. The treatment response rate was determined by investigators as defined by the International Myeloma Working Group Uniform Response Criteria.

The primary end point of event-free survival (EFS) was defined by progression, death, or change in line of therapy. Secondary outcomes were objective response rate (ORR) and rate of treatment discontinuation due to adverse events (AEs).

Findings

Although patients were well matched for age, gender, and stage, Landgren pointed out that information on cytogenetics was missing for 71% of the KRd group and 41% of the VRd group. Looking only at those patients for whom cytogenetic information was available, there was an improvement in high-risk cytogenetics in the KRd group. The rate of transplantation was 52% in the KRd group and 70% in the VRd group.

Median follow-up was 11.5 months for the KRd group and 41.9 months for the VRd group. There was a 65% reduced risk of EFS, the primary outcome, in the KRd group versus VRd (HR, 0.35; 95% CI, 0.19-0.64; $P<.001$). In landmark analyses, the 12-month EFS in the KRd group was 90% versus 78% for VRd; at 18 months, EFS was 87% versus 72%, respectively.

Similarly, EFS for patients treated with KRd was significantly longer, independent of transplant status. For patients receiving a transplant, the hazard ratio was 0.49 for KRd (n = 78; 95% CI, 0.25-0.97; $P = .037$) versus VRd (n = 103). For those who did not have a transplant, the hazard ratio was 0.46 for KRd (n = 73; 95% CI, 0.23-0.91; $P = .022$) versus VRd patients (n = 47).

The best clinical response at 12 months was determined by individual investigators at their sites. Response rates were higher in patients with KRd than VRd: ORR was 80% versus 64%, respectively; very good partial response or better was 70% versus 54%, respectively; and complete response or better was 35% versus 14%, respectively.

Landgren added that because this was not a clinical trial, no traditional safety data would be captured. Instead, investigators looked at patients who had AEs that led to treatment discontinuation, the best method that could be used in this type of study to analyze issues with toxicity. There was, ultimately, a very low rate of treatment discontinuation due to AEs and no significant difference between the 2 treatments, he said, with the overall treatment discontinuation rate from AEs at 3.4% for each arm. Discontinuation of treatment due to AEs during the first 6 to 12 months of treatment were similar between treatment groups.

This study was subject to several limitations, as it was an unblinded, prospective cohort case-controlled study, relying on clinician-assessed responses. Missing data prevented matching treatment groups for ECOG performance status and cytogenetic risk. There were slight differences in patient characteristics between the 2 groups. A higher percentage of patients treated with VRd received a transplant. Among patients in the KRd group with available data on cytogenetics, more high-risk disease was presented. Other limitations included a shorter median follow-up time for the KRd group and a lack of full safety data.

Although this analysis from the CoMMpass study shows that KRd compares favorably with VRd in patients with NDMM, data from ongoing randomized trials are needed to definitively determine the superiority of KRd.[2,3]

Sagar Lonial, MD, of Winship Cancer Institute of Emory University in Atlanta, Georgia, pointed out that as principal investigator of the CoMMpass trial, he was aware of the inclusion of data from a group of patients in a randomized trial of KRd, so those patients were subject to eligibility criteria and probably have different outcomes than ineligible patients. Landgren agreed that this was a fair criticism and reflects the limitations of a prospective cohort study. "The full truth will come from the randomized trial," he said. ◆

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Lenalidomide/Rituximab Improves Progression-Free Survival in Indolent Non-Hodgkin Lymphoma

Jason M. Broderick

THE R² REGIMEN OF LENALIDOMIDE (Revlimid) plus rituximab (Rituxan) reduced the risk of disease progression or death by 54% versus rituximab alone in patients with relapsed/refractory indolent non-Hodgkin lymphoma (NHL).

Results from the phase 3 AUGMENT trial presented at the 2018 American Society of Hematology Annual Meeting showed that at a median follow-up of 28.3 months, the median progression-free survival (PFS) per independent review was 39.4 months (95% CI, 22.9-not evaluable) with R² versus 14.1 months (95% CI, 11.4-16.7) with rituximab alone (HR, 0.46; 95% CI, 0.34-0.62; *P* <.0001).

By investigator assessment, the median PFS was 25.3 months (95% CI, 21.2-not evaluable) versus 14.3 months (95% CI, 12.4-17.7), respectively (HR, 0.51; 95% CI, 0.38-0.69; *P* <.0001).

Overall response rate (ORR) was also significantly improved with the combination. The ORR per independent review was 78% with R² versus 53% with rituximab alone (*P* <.0001). The 78% ORR rate in the R² arm was composed of a 44% complete response rate and a 34% partial response rate.

"AUGMENT met its primary end point, as R² demonstrated statistically significant and clinically relevant superiority over rituximab/placebo for the primary end point of PFS," said lead study author John P. Leonard, MD, associate dean for Clinical Research and Richard T. Silver Distinguished Professor of Hematology and Medical Oncology at Weill Cornell Medicine and NewYork-Presbyterian Hospital. "R² represents an important new treatment option in patients with previously treated indolent NHL."

The double-blind, phase 3 AUGMENT trial included 358 patients with relapsed/refractory follicular lymphoma (n = 295) or marginal zone lymphoma (MZL; n = 63) in need of treatment. Patients had to have received at least 1 prior chemotherapy, immunotherapy, or chemoimmunotherapy regimen, and they could not be rituximab-refractory.

Patients were randomized to rituximab at 375 mg/m² on days 1, 8, 15, and 22 of cycle 1, and day 1 of cycles 2 through 5, plus either 20 mg of lenalidomide daily on days 1 through 21 every 28 days for up to 12 cycles (n = 178) or placebo (n = 180).

Patient characteristics at baseline were well balanced overall between the 2 arms. About 60% of patients were aged ≥60 years. More than 70% of patients had advanced-stage disease at study entry. About 50% of patients had high tumor burden per the GELF criteria. Approximately 83% of patients in each arm had follicular lymphoma, with the remaining 17% having MZL.

The FLIPI scores in the R² arm included low (29%), intermediate (31%), and high (39%). The respective rates were 37%, 32%, and 30% in the placebo arm.

In the R² arm, 57% of patients had received 1 prior systemic regimen, 17% had received 2, and 25% had received ≥3. In the control arm, the corresponding rates were 54%, 23%, and 23%, respectively. Eighty-five percent of patients in the R² arm and 83% of patients in the placebo arm had prior rituximab. About 75% of patients in each arm had received a prior rituximab-containing chemotherapy regimen. Thirty-seven percent of patients in the R² arm and 42% of patients in the placebo arm had progressed within 2 years of their last regimen.

The PFS benefit with R² was sustained across almost all prespecified subgroups, regardless of age, disease histology, whether they had prior rituximab, number of prior regimens, time since last antilymphoma therapy, geographic region where treatment was received, chemoresistance status, or tumor burden status.

Leonard noted, however, that the single exception in which the PFS advantage in a subgroup was not consistent with the overall population was the subgroup of patients with MZL. In this group, the HR for PFS was 1.00 (95% CI, 0.47-2.13). "This relates to the fact that there were roughly 30 patients in each arm with MZL, which limits these comparisons," said Leonard.

Overall survival (OS) data across the entire population showed that at a median follow-up of 28.3 months, the HR for OS was 0.61 (95% CI, 0.33-1.13). The 2-year OS rate was 93% (95% CI, 87%-96%) for R² and 87% (95% CI, 81%-92%) for rituximab alone.

In a prespecified subgroup analysis of patients with follicular lymphoma, at a median follow-up of 28.3 months, the HR for OS was 0.45 (95% CI, 0.22-0.91; *P* = .02). The 2-year OS rate was 95% (95% CI, 90%-98%) for R² and 86% (95% CI, 79%-91%) for rituximab alone.

Thirty percent of patients in the R² arm discontinued treatment early compared with 39% of patients in the placebo arm. The primary cause of discontinuation was disease progression, at 12% in the R² arm versus 30% in the control arm. Adverse events (AEs) led to discontinuation in 8% of the R² group versus 4% of the placebo group. Among patients receiving lenalidomide, 66% had at least 1 AE-related dose interruption.

"The main grade 3/4 AE difference [between the 2 arms] in adverse events [was] in neutropenia," said Leonard.

However, the neutropenia generally did not result in febrile neutropenia, which affected just 3% of patients in the R^2 arm. Also, "venous and arterial thromboembolic AEs were relatively low and similar in both arms," said Leonard. Of note, 6 patients in the R^2 arm and 10 patients in the placebo arm had secondary malignancies.

In a discussion after his presentation, Leonard was asked where he sees the R^2 regimen fitting into the treatment landscape for relapsed/recurrent follicular lymphoma, given that several agents are already approved in this setting.

"Obviously, there are other agents approved for relapsed/recurrent follicular lymphoma in different settings. There is a meaningful percentage of patients who are currently treated with single-agent rituximab. These data suggest that many of those patients, instead, could benefit from the combination of R^2," said Leonard. "How this compares with chemotherapy, as well as other approaches, such as PI3-kinase inhibitors, really depends on the individual situation of the patient," he added. ◆

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New Prediction Model Improves Personalized Insight Into Myelodysplastic Syndromes Survival

Kristie L. Kahl

AN APPROACH USING MACHINE learning to analyze genomic and clinical data from patients with myelodysplastic syndromes (MDS) could replace the current gold standard for predicting how long patients may live with the disease, according to Aziz Nazha, MD, in a presentation during the 2018 American Society of Hematology Annual Meeting.

"A random survival forest (RSF) algorithm was used to build the model, in which clinical and molecular variables are randomly selected for inclusion in determining survival, thereby avoiding the shortcomings of traditional Cox stepwise regression in accounting for variable interactions," wrote Nazha and his team. "Survival prediction is thus specific to each patient's particular clinical and molecular characteristics."

The machine learning model outperformed the International Prognostic Scoring System (IPSS) and Revised IPSS (IPSS-R) in predicting survival outcomes and risk for acute myeloid leukemia (AML) transformation among a training cohort of 1471 patients. Accuracy, as assessed by concordance index, showed the machine learning model correctly predicted overall survival (OS) 74% of the time and leukemia-free survival (LFS) 81% of the time compared with 66% and 73%, respectively, for IPSS, and 67% and 73% for IPSS-R.

In addition, the researchers conducted several feature extraction analyses to identify the most important variables that impacted patients' outcomes, as well as the least number of variables that produced the best prediction. From most important to least, variables included cytogenetic risk categories by IPSS-R, platelets, mutation number, hemoglobin, bone marrow blast percentage, 2008 World Health Organization diagnosis, white blood cell count, age, absolute neutrophil count, absolute lymphocyte count, TP53, RUNX1, STAG2, ASXL1, absolute monocyte counts, SF3B1, SRSF2, RAD21, secondary versus de novo MDS, NRAS, NPM1, TET2, and EZH2.

During his presentation at the meeting, Nazha, of the Leukemia Program at the Cleveland Clinic's Taussig Cancer Institute, demonstrated how the clinical and mutational variables can be entered into a Web application that can run the trained model and provide OS and AML transformation probabilities at different time points specific for each patient. However, the model is not yet available for clinician use.

With these variables, the machine learning model also outperformed IPPS and IPPS-R in predicting OS and LFS by mutations only, mutations plus cytogenetics, and mutations plus cytogenetics plus age. The researchers noted that the addition of mutational variant allelic frequency did not significantly improve prediction accuracy.

Similarly, in the 831 patients included in the validation cohort, the RSF algorithm predicted OS 80% of the time and LFS 78% of the time.

Need for Personalization

Patients diagnosed with MDS show a wide range of symptoms, and the disease can lead to anemia, bleeding, or

infection. Prognosis can range widely as well, from just a few months to decades. However, the MDS population is also at a high risk (approximately one-third) for developing AML.

Therefore, Nazha noted that both the patient and the clinician can derive benefit from this model. "Prognosis in MDS, and oncology in general, is among the most important things we can do because after diagnosis, the next step in treating the patient is to stage their disease or define the risk," he said.

"That is extremely important for patients, because [explaining their prognosis] helps to set up their expectation early to help them to understand their disease and what to expect of their journey," he added. "For clinicians, it is equally important because all of our guidelines and treatment recommendations are based on risk stratification, which includes low and high risk of progression to AML."

In turn, understanding a patient's prognosis can also affect treatment options. For example, high-risk patients are generally treated with stem cell transplant, while low-risk patients undergo treatment with fewer associated risks. However, if risk is identified inaccurately—as happens in the cases of one-third of patients utilizing the IPSS-R system—then the treatment is incorrect. "If we label the disease as high risk and the disease might be lower risk, we're changing the management of these patients, and we are now overtreating them; and vice versa, if you have a patient [who] is lower risk, but they are high risk, that becomes a problem," Nazha said.

To improve upon the model, the researchers are gathering feedback from clinicians to incorporate more outcomes, such as quality of life, into it. They are also developing ways to update the assessment of risk in response to changing conditions, such as when new test results are available or treatments are completed.

"This project started out of a frustration voiced by many of my patients who want to know what their own risk is and how their prognosis might differ from that of other patients. We wanted to build a personalized prediction tool that can give insights about a specific outcome for a specific patient," Nazha said in a news release. "Improving and personalizing our prognostic models can help to delineate patients who are at higher versus lower risk—which is particularly challenging for those who fall into the intermediate range—and match them with the appropriate treatment." ◆

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Carfilzomib Plus Pomalidomide and Dexamethasone is Effective Salvage Therapy for Bortezomib- and Lenalidomide-Resistant Multiple Myeloma

Lynne Lederman, PhD

PIETER SONNEVELD, MD, PHD, presented preliminary results of the phase 2 European Myeloma Network (EMN) 011 trial (NTR5349 and EudraCT 2013-003265-34) of carfilzomib, pomalidomide, and dexamethasone (KPd) in patients with multiple myeloma refractory to bortezomib and lenalidomide.[1] Sonneveld, of the Erasmus MC Cancer Institute, Rotterdam, Netherlands, noted that such patients currently have no available effective therapy.

In Europe, patients now eligible for transplantation usually receive induction treatment with an immunomodulatory drug (IMiD) and a proteasome inhibitor (PI)—primarily bortezomib plus thalidomide and dexamethasone; or alternately, bortezomib, cyclophosphamide, and dexamethasone (VCD). In some countries, patients may receive bortezomib plus lenalidomide and dexamethasone (VRd). Induction is followed by transplantation and consolidation with the same regimen, followed by lenalidomide maintenance for 1 to 2 years, or until disease progression. "This is the situation that many patients are in, and they may progress on lenalidomide maintenance or maybe before [maintenance] without a strict strategy for the second-line therapy," Sonneveld said.

Trial Aims and Results

The aims of the EMN011 trial were to evaluate salvage treatment with a next-generation PI and IMiD. Carfilzomib plus

Rivaroxaban May Reduce Blood Clot Risk During Active Systemic Cancer Therapy

Kristie L. Kahl

RIVAROXABAN (XARELTO) MAY SIGNIFICANTLY reduce venous thromboembolism (VTE) occurrence among patients actively being treated with systemic therapy for cancer, according to results from the phase 3b CASSINI trial presented at the 2018 American Society of Hematology Annual Meeting.

However, study results showed that the agent failed to significantly reduce VTE events during the primary analysis period of 180 days. Alok A. Khorana, MD, professor of medicine, Cleveland Clinic Lerner College of Medicine, Ohio, explained this was due mainly to a large proportion of patients who stopped taking the drug before the end of the 6-month period.

"The problem was that this is a cancer patient population getting chemotherapy, many of whom are switching chemotherapy drugs or who progress on chemotherapy and switch to a different clinical drug," he added. "So, about half of patients—in the entire study population—did not take the drug for the full 6 months."

The international, multicenter, randomized, double-blind, placebo-controlled superiority study compared the efficacy and safety of rivaroxaban with placebo for thromboprophylaxis in 1080 ambulatory patients with cancer. The investigators aimed to assess the use of the direct oral anticoagulant (DOAC), administered as a daily pill, and to investigate the therapy's use when restricted to patients at high risk for VTE, initiating a new systemic regimen to determine VTE risk, defined as Khorana score ≥2.

"About 10 years ago, my research colleagues and I developed a score that helps predict patients who are at risk for getting a blood clot, and that is helpful because if we target prevention toward high-risk patients, then the benefit would be greater and so the clinical benefit to patients would be greater," Khorana said. "So, that was really our hypothesis going into this clinical trial."

In total, 841 patients were randomized 1:1 to receive either 10 mg rivaroxaban once daily (n = 420) or placebo (n = 421) up to day 180. Deemed ineligible were 49 patients with deep vein thrombosis (DVT) at baseline and another 190 who screen-failed for other reasons.

A composite of events that included objectively confirmed symptomatic or asymptomatic lower-extremity proximal DVT, symptomatic upper- or lower- extremity distal DVT, symptomatic or incidental pulmonary embolism, and VTE-related death served as the primary end point. Major bleeding, as defined by the International Society on Thrombosis and Haemostasis, was the primary safety end point.

A composite of events in the primary efficacy end point occurred in 25 patients (6%) in the rivaroxaban arm compared with 37 (8.8%) in the placebo arm (HR, 0.66; 95% CI, 0.40-1.09; P = .101). However, as Khorana had noted, this result was predictable given that 38.7% of patients discontinued treatment with the DOAC during the 6-month period and went on to experience a clot event. "It's not unexpected, because we know that if patients are not taking the drug, then you obviously won't prevent a clot," he added.

When the investigators compared efficacy outcomes using a prespecified analysis of all randomized patients during the on-treatment period of patients actually taking the drug, events occurred in 11 (2.6%) patients in the treatment arm compared with 27 (6.4%) in the placebo arm (HR, 0.40; 95% CI, 0.20-0.80; P = .007).

As a secondary efficacy end point, the investigators conducted a prespecified analysis of the composite of the primary end point with the addition of arterial and visceral thromboembolic events in the up-to-day-180 observation period. The rivaroxaban arm demonstrated significantly fewer events compared with the placebo arm (6.9% vs 10.7%; HR, 0.62; 95% CI, 0.39-0.99; P = .04).

During both time periods, the investigators also evaluated the number needed to treat, or "how many patients have to take the drug to prevent a blood clot for 1 of them not to have a blood clot," Khorana explained. In the up-to-day-180 period, 35 patients would have had to have been treated to prevent 1 blood clot, compared with 26 patients during the on-treatment period. "And then if you include some of these additional secondary end points (arterial plus visceral VTE), it is actually only 20," he added. "So, the clinical benefits continue to improve when you include secondary end points and the [on-treatment] end point."

All-cause mortality occurred in 20.0% of patients in the rivaroxaban group and 23.8% in the placebo group (HR, 0.83; 95% CI, 0.62-1.11; P = .213); while a prespecified composite of the primary end point with all-cause mortality occurred in 23.1% and 29.5%, respectively (HR. 0.75; 95% CI, 0.57-0.97; P = .03).

Safety analyses were conducted for the on-treatment period only for patients who received at least 1 dose of study drug (n = 405) or placebo (n = 404). Major bleeding occurred in 8 (2%) and 4 patients (1%), respectively (HR, 1.96; 95% CI, 0.59-6.49; P = .265); while 11 (2.7%) and

8 (2%) patients, respectively, experienced clinically relevant nonmajor bleeding (HR, 1.34; 95% CI, 0.54-3.32; P = .53). Sites of major bleeding included gastrointestinal (n = 8), intraocular (n = 2), and intracranial (n = 2), while 1 fatal bleed occurred in the rivaroxaban arm. The investigators noted that adverse events were comparable between groups.

"Because nearly one-third of these events were at baseline, before patients have even started on chemotherapy, we wonder if baseline screening should be considered in patients' start treatment with systemic therapy," Khorana said. "Regardless, we believe our findings should inform future recommendations regarding thromboprophylaxis for higher-risk ambulatory cancer patients." ◆

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Venetoclax With Hypomethylating Agents Shows Promise in Acute Myeloid Leukemia for Patients Ineligible for High-Dose Chemotherapy

MORE THAN 70% OF older patients ineligible for intensive chemotherapy for acute myeloid leukemia (AML) had complete responses (CRs) to venetoclax (Venclexta) combined with hypomethylating agents (HMAs), preliminary results from clinical trials have shown.

CR rates (including those in patients with incomplete hematologic recovery [CRi]) were similar whether venetoclax was paired with azacitidine or decitabine. The majority of patients had response durations of ≥12 months with the combination therapy, as reported at the 2018 American Society of Hematology Annual Meeting in San Diego.[1]

"Venetoclax plus hypomethylating agents was well tolerated in previously untreated older patients with AML who were ineligible for intensive chemotherapy," said Daniel A. Pollyea, MD. "Deep and durable responses were observed in a majority of patients."

In general, baseline genetic mutations and cytogenetic risk did not affect response to the combination therapy, added Pollyea, a clinical director of Leukemia Services and an associate professor of medicine at the University of Colorado School of Medicine in Aurora.

In another preliminary clinical evaluation, venetoclax plus low-dose cytarabine led to complete responses in more than half of a mixed group of older patients with AML, including a 71% response rate in patients with previously untreated disease.[2]

AML primarily affects older adults (median age 68 years at diagnosis), many of whom have limited treatment options and are ineligible for or refractory to intensive induction chemotherapy, Pollyea noted in the introduction to his presentation. BCL-2, the target of venetoclax, has antiapoptotic effects and is overexpressed in AML and AML stem cells. Preliminary data from a phase 1b clinical trial showed promising clinical activity with venetoclax/HMA treatment among older patients with untreated AML.[3]

These results support the recent FDA accelerated approval for venetoclax in combination with azacitidine, decitabine, or low-dose cytarabine for newly diagnosed AML in patients aged ≥75 years or in younger patients who have comorbidities that preclude use of intensive therapy.

Pollyea reported findings from a phase 1b dose escalation/expansion study evaluating venetoclax 400 mg to 1200 mg in combination with either azacitidine or decitabine in older patients with untreated AML. His report focused on patients treated with 400 mg of venetoclax, which trial investigators identified as the recommended phase 2 dose.[4]

The analysis included 115 patients, 84 who received azacitidine and 31 who received decitabine as the HMA component. Eligibility criteria included a minimum age of 60 years; the median ages were 75 years and 72 years for the azacitidine and decitabine subgroups, respectively.

Overall, 31 of the 115 patients had <30% bone marrow blasts at baseline, 43 had 31% to <50%, and 41 had ≥50%. Mutational analyses identified TP53 in 27 patients, IDH1/2 in 25, FLT3 in 14, and NPM1 in 17. Cytogenetic risk was intermediate in 66 patients and poor in 48. A total of 30 patients had secondary AML.

The primary outcome was response rate, limited to those patients who attained a CR/CRi. The results showed a 71% response rate for patients who received azacitidine with venetoclax (27% with CRi) and 74% in the decitabine group (19% with CRi).

Total response (irrespective of the HMA agent used) did not differ substantially by cytogenetic risk category, AML type (de novo or secondary), or baseline mutation status.

The median time to CR was 1.2 months (range, 0.7-5.5) in the azacitidine group and 1.9 months (range, 0.9-4.6) in the decitabine group. Pollyea noted that the time to response was lower than that typically seen in older patients with AML treated with other therapies. As a result, patients treated with venetoclax-containing regimens probably should have earlier response assessments.

The venetoclax/azacitidine group had a median response duration of 21.2 months (95% CI, 14.4-30.2) and a 12-month event-free rate of 69% (95% CI, 52%-80%) after achieving a CR/CRi. The decitabine group had a median response duration of 15 months (95% CI, 5.0-22.5) and a 12-month event-free rate of 57% (95% CI, 32%-76%).

Analysis of all 115 patients yielded a median overall survival (OS) of 16.9 months and 16.2 months with azacitidine and decitabine, respectively, and the 12-month event-free survival (EFS) rates were 57% and 61%, respectively.

When survival and EFS were analyzed by response status, CR was associated in the azacitidine group with a median OS of 40.3 months and a 12-month EFS of 72%; those declined to 4.5 months and 19% for patients who did not attain a CR. In the decitabine group, median survival was 18.2 months and the 12-month EFS was 74% for responders, while it was 4.8 months and 28% for all other patients.

Data analysis for the phase 1/2 venetoclax/low-dose cytarabine trial included 82 patients who had a median age of 74 years. Almost half (n = 40) had secondary AML, 24 had prior exposure to an HMA, and 41 patients had received a CYP3A inhibitor, said Stephen A. Strickland Jr, MD, MSCI, clinical director, Acute Leukemia, Vanderbilt–Ingram Cancer Center, Nashville, Tennessee.

The venetoclax dose was escalated from 50 to 400 mg over 5 days, and starting on day 6, patients received 600 mg. Patients received cytarabine 20 mg/m^2 on days 1 to 10. With that regimen, 1 patient developed laboratory tumor lysis syndrome (TLS), but no patient had clinical TLS, said Strickland.

The response rate (CR, including patients with CRi) was 54%. More variation by baseline characteristics was observed as compared with the data reported by Pollyea. Patients with intermediate cytogenetics had a 63% response rate, compared with 42% in the high-risk group. Prior HMA exposure was associated with a response rate of 33%, increasing to 62% with no HMA treatment history. Patients with de novo AML had a response rate of 71%, versus 35% for patients with secondary AML.

The median time to first response was 1.4 months (range, 0.8-14.9), and the median time to best response was 2.8 months (range, 0.8-22.4).

The median OS was 10.1 months (95% CI, 5.7-14.2), which included a 6% mortality rate during the first 30 days. The 12-month OS rate was 100% in patients who had a CR, 73% for patients with CRi, and 5% for all other patients. The median OS had yet to be reached for patients with CR and hematologic recovery; it was 18.4 months for all patients with a CR and 3.5 months for all others.

The most common treatment-emergent adverse events (TRAEs; all grades) were nausea (70%), diarrhea (49%), hypokalemia (48%), fatigue (43%), febrile neutropenia (43%), and thrombocytopenia (38%). Grade 3/4 TRAEs included febrile neutropenia (42%), thrombocytopenia (38%), decreased white blood cells (34%), neutropenia (27%), and anemia (27%). The most frequent serious AEs were anemia (31%), febrile neutropenia (27%), pneumonia (10%), and sepsis (7%).

"Venetoclax plus low-dose cytarabine demonstrated a tolerable safety profile," said Pollyea. "The response rate was 54% in a group of patients who were ineligible for intensive chemotherapy, including a 71% and a median OS of 16.9 months in patients with de novo AML.

"The high rates of remission and low rates of early mortality make venetoclax plus low-dose cytarabine an attractive option in these patients." ◆

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Recently Approved Higher-Dose Carfilzomib Improves Survival and Time to Next Treatment Compared With Initially Approved Dose

Lynne Lederman, PhD

SUMEET PANJABI, PHD, presented real-world evidence that optimizing carfilzomib dosing intensity could benefit patients with multiple myeloma treated with at least 3 doses of carfilzomib for any line of therapy.[1] The objective of the study was to determine the impact of carfilzomib (K) plus dexamethasone (d; Kd) dosing in real-world overall survival (OS) and time to next treatment (TTNT). Panjabi, of Amgen in South San Francisco, California, described the latter as both a clinically and patient-relevant end point. Weekly Kd doses of >120 mg and ≤120 mg were compared cumulatively, Panjabi noted.

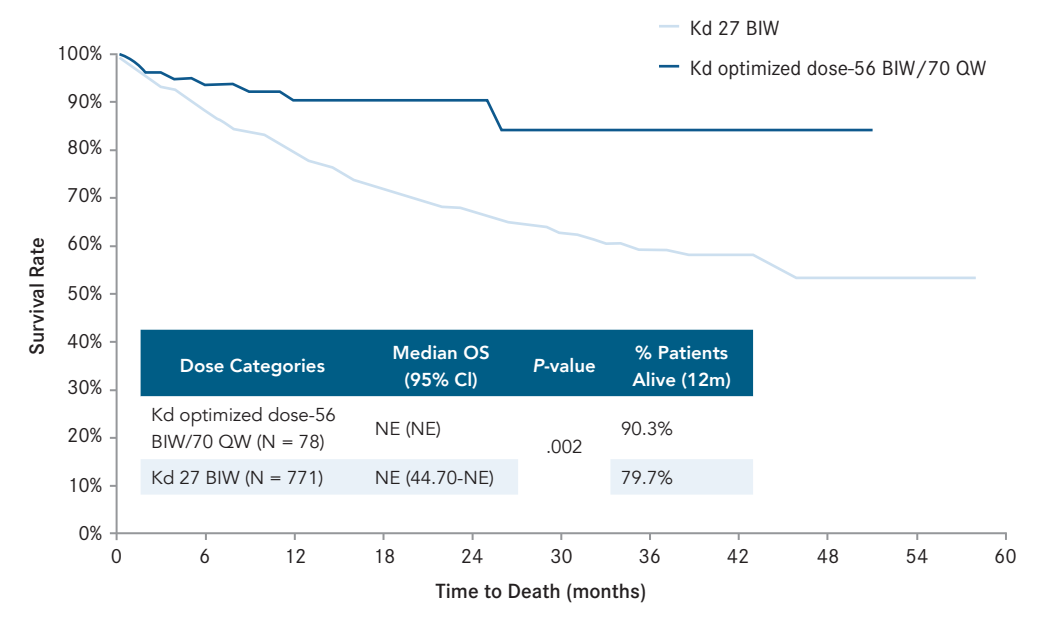
The rationale was determined by the approval of carfilzomib to include a once-weekly dosing option when combined with dexamethasone for patients with relapsed or refractory multiple myeloma. The administration of Kd 70 mg/m^2 once weekly was recently approved based on the ARROW trial, showing the superiority of this dose relative to the "legacy dose" of 27 mg/m^2 twice weekly K, approved in 2012. In 2016, a K dose of 56 mg/m^2 twice weekly was approved after the ENDEAVOR trial, which showed the superiority of Kd over bortezomib plus dexamethasone. The dose of 56 mg/m^2 twice weekly and 70 mg/m^2 once weekly provided a cumulative weekly dose of >120 mg K, while the legacy dose of 27 mg/m^2 twice weekly provided a cumulative weekly dose of ≤120 mg of K.

Patients aged ≥18 years who received a regimen of ≥3 Kd doses between January 1, 2013, and October 31, 2017, through any line of therapy were identified from IQVIA's Oncology US electronic medical records (EMR) database. All patients had a 12-month preindex period, during which baseline characteristics were assessed. Postindex follow-up was variable. Outcome measures included OS and TTNT (time from Kd initiation until start of a new regimen not containing K).

Of 19,970 patients with a diagnosis of myeloma during the selection window, 1728 received Kd and had adequate data available during that period. Of these, 1469 received ≥3 Kd doses and formed the patient sample for the study. This group included 129 patients (8.8%) who received K 56 mg/m^2 twice weekly or 70 mg/m^2 once weekly (higher-dose group), and 1340 patients (91.2%) who received the legacy K dose of 27 mg/m^2 twice weekly (lower-dose group).

There were significant differences between the groups in baseline characteristics. Individuals in the higher-dose group tended to be younger (mean age, 63.5 vs 67.0 years; $P = .0003$), male (67.4% vs 55.2%; $P = .007$), and have a lower Charlson Comorbidity Index score (0.2 vs 0.5; $P = .029$). There were no significant differences between dose groups for

FIGURE. Overall Survival Among Patients on Kd 56 mg/m^2 Twice Weekly or 70 mg/m^2 Once Weekly Versus 27 mg/m^2 Twice-Weekly[a]



Kd indicates carfilzomib plus dexamethasone; OS, overall survival.

[a]Patients include those with recorded deceased or alive status.

peripheral neuropathy, pneumonia, neutropenia, hypercalcemia, renal impairment, anemia, bone-related condition, cardiac dysfunction, or receipt of hydration.

The higher-dose group received a significantly higher mean dose of Kd: 155.6 mg weekly versus 84.9 mg weekly (P <.0001). There were no significant differences in mean Kd duration (approximately 6 months) or in the number of lines of therapy prior to Kd.

A significantly greater proportion of patients were alive at 12 and 24 months follow-up in the higher-dose group, as shown in the **Figure**. At 12 months, OS was 90.3% in the higher-dose group versus 79.7% in the lower-dose group (HR, 0.348; 95% CI, 0.172-0.702; P = .002).

The risk of mortality in the higher dose group was approximately 64% lower when adjusted for differences in baseline characteristics. Additionally, the higher treatment dose was associated with higher survival probability, whereas hypercalcemia and anemia at baseline were associated with increased risk of death for both groups.

A significantly greater proportion of patients taking the higher dose compared with those on the lower dose remained on treatment at 12 months (68.0% vs 55.1%, respectively) and at 24 months (39.7% vs 31.6%, respectively). Median TTNT was significantly higher at 17.5 months for the higher-dose group versus 13.2 months for the lower-dose group (HR, 0.696; 95% CI, 0.509-0.953; P = .023).

Patients in the higher-dose group were observed to have a 33% lower risk of treatment progression than those in the lower-dose group. Peripheral neuropathy at baseline was associated with a lower probability of progression to the next treatment.

Panjabi noted that the results were limited to data provided by physicians that were captured in the IQVIA Oncology EMR database, representing a possible limitation. As an oncology-specific database was used in this analysis, comorbidities diagnosed by a practitioner, rather than an oncologist may not have been included in the database and therefore may be underreported.

Panjabi concluded that patients who received the higher dose of Kd compared with the lower dose lived longer and had a longer progression time to subsequent therapies. Therefore, these findings suggest that the higher Kd dose in a real-world setting confers additional benefits in patients with multiple myeloma.

During the discussion, an attendee asked if the study's patient population reflected that of the general US population of patients with multiple myeloma,and how cost may have contributed to dosing. Specifically, since almost 20,000 patients were in the study, and only 129 were on the higher Kd dose, the questioner wondered whether the results were of US practice. Panjabi agreed that the sample size was small, and that the team intends to conduct follow-up studies evaluating a broader sample of patients. ◆

REFERENCE

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