Supplement to
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UPDATES IN Multiple Myeloma

Findings from ASH Annual Meeting and Exposition

POLLUX

Daratumumab yields durable response in relapsed, refractory disease

Triplet combinations with pomalidomide improve response

Overall responses nearly doubled with three-drug vs. two-drug regimens containing pomalidomide

Tourmaline-MM3

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Bisphosphonates underused in older patients

Only half of Medicare beneficiaries with multiple myeloma receive bone-modifying agents

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Research at ASH reveals progress, unmet needs in multiple myeloma

The 60th ASH Annual Meeting and Exposition, held in San Diego from Dec. 1-4, 2018, brought together an international community of more than 25,000 hematology professionals who were given the opportunity to review thousands of scientific abstracts with updates in hematology at the conference.

Multiple myeloma was a critical area of focus at this year's meeting. A late-breaking abstract highlighted interim results of an international phase 3 trial that showed the addition of daratumumab, a human monoclonal antibody that targets CD38, to lenalidomide and dexamethasone nearly halved the risk for disease progression or death among transplant-ineligible, newly diagnosed patients.

Additional trials further demonstrated the promise of novel immunotherapy agents and explored optimal treatment regimens for patients. Despite progress, researchers also described a need to improve patient care, particularly by increasing the use of bisphosphonates and other supportive care services in elderly patients with multiple myeloma.

This *HemOnc Today* supplement provides readers with an overview of the most noteworthy — and potentially practice-changing — data on multiple myeloma presented at the ASH Annual Meeting and Exposition. Perspectives from physicians in the hematology communities provide further insight into the impact these findings may have in practice. — *The Editors of* HemOnc Today.

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Racial disparities seen in supportive care use

Study results showed that elderly adults with multiple myeloma in the United States did not fully utilize available supportive care services aimed at bone health and infection prevention, with significant racial disparities seen in the receipt of this care. "Patients with multiple myeloma are living longer than before, and it has become more relevant to focus on quality-of-life issues such as minimizing disease-related adverse events and toxic effects of therapy," **Smith Giri, MBBS,** clinical fellow in Yale Cancer Outcomes, Public Policy and Effectiveness Research Center and section of hematology at Yale University School of Medicine, told *HemOnc Today*. "Various supportive care measures focused on bone health and infection prevention that have been shown to be safe and effective are uniformly recommended. Despite these recommendations, the extent to which these get adopted in real-world clinical practice remains unknown."

> **"Patients with multiple myeloma are living longer than before, and it has become more relevant to focus on quality-of-life issues such as minimizing disease-related adverse events and toxic effects of therapy."**
> SMITH GIRI, MBBS

Giri and colleagues consulted the SEER database to identify 1,569 Medicare beneficiaries aged older than 65 years (median age, 74 years; 47% men; 73% non-Hispanic white) who were diagnosed with multiple myeloma between 2008 and 2013.

The researchers sought to determine the percentage of patients receiving guideline-consistent supportive care treatment, defined as: bisphosphonate treatment (zoledronic acid or pamidronic acid) within the first 12 months of diagnosis; receipt of influenza vaccine in the first influenza season after diagnosis; and treatment with antivirals (acyclovir and valacyclovir) in patients undergoing bortezomib therapy.

The researchers then evaluated possible predictors of supportive care utilization, including patient characteristics (age, gender, race/ethnicity, comorbidities, disabilities, diagnosis of chronic kidney disease, socioeconomic status and year of diagnosis); provider experience (number of multiple myeloma patients treated at a 12-month review); and type of facility (hospital outpatient vs. community setting).

Results showed only 66% of Medicare patients on active treatment for multiple myeloma received bisphosphonates within 1 year of diagnosis. During the first influenza season after diagnosis, 53% of patients were vaccinated, and 44% received preventive antivirals while receiving bortezomib.

In a sensitivity analysis, Giri and colleagues found that 48% of patients with preexisting chronic kidney disease received bisphosphonates, whereas 72% without preexisting chronic kidney disease received bisphosphonates.

Multivariable analysis revealed that the predictors of bisphosphonate nonuse included advanced age (OR for 85+ years vs. 66-69 years = 0.37; 95% CI, 0.23-0.58), non-Hispanic black (OR = 0.51; 95% CI, 0.34-0.76) and Hispanic ethnicity (OR = 0.56; 95% CI, 0.35-0.91), and elevated comorbidity index (Elixhauser index of 3+ vs. 0, OR = 0.41; 95% CI, 0.29-0.57).

Significant predictors of influenza vaccination nonuse included non-Hispanic black ethnicity (OR = 0.49; 95% CI, 0.34-0.7), residence in the West vs. Midwest (OR = 0.54; 95% CI, 0.38-0.75), having Medicaid dual coverage (OR = 0.66; 95% CI, 0.49-0.89), and lower comorbidity score (Elixhauser index of 3+ vs. 0, OR = 1.44; 95% CI, 1.07-1.93).

Predictors of antiviral prophylaxis nonuse included earlier years of diagnosis (global $P < .01$, with increasing OR for later years) and higher comorbidity index (for Elixhauser index of 3+ vs. 0, OR = 0.4; 95% CI, 0.24-.0.67). "We can learn from our study that making guidelines alone is not enough," Giri told *HemOnc Today.* "Various strategies need to be implemented to ensure that these supportive care measures actually get adopted in routine clinical practice. Incorporating these measures into quality metrics, development of decision support tools, and other interventions focused on high-risk patients may help minimize these disparities in the future." – *by Jennifer Byrne* ■

Reference:
Giri S, et al. Abstract 978. Presented at: ASH Annual Meeting and Exposition; Dec. 1-4, 2018; San Diego

Disclosure: Giri reports no relevant financial disclosures.

Originally published on Healio.com/HemOnc | January 5, 2019

Triplet combinations with pomalidomide improve response vs. doublet combinations

Triplet combination regimens containing pomalidomide nearly doubled response rates compared with doublet combination regimens of pomalidomide in patients with relapsed or refractory multiple myeloma, according to results of a systematic review and meta-analysis.

Adeela Mushtaq, MD, physician and medical resident at the University of Pittsburgh Medical Center, and colleagues found that pomalidomide (Pomalyst, Celgene) and low-dose dexamethasone plus bortezomib (Velcade, Millennium/Takeda) or carfilzomib (Kyprolis, Amgen) were associated with the highest overall response rates among the triplet combination regimens analyzed.

"Pomalidomide has distinct anticancer, antiangiogenic and immunomodulatory properties and has demonstrated synergistic antiproliferative activity in combination regimens," the researchers wrote. "Our study provides useful insight into relative efficacy of various pomalidomide regimens for the treatment of [relapsed or refractory multiple myeloma] patients."

Mushtaq and colleagues conducted a comprehensive literature search of phase 2 and 3 studies evaluating the efficacy of various pomalidomide-based therapies to identify the optimal regimen in relapsed and refractory multiple myeloma. Their analysis included 35 studies involving 4,623 patients who received at least two prior treatment regimens. Most patients were refractory to lenalidomide (Revlimid, Celgene). The most common regimen studied was pomalidomide plus low-dose dexamethasone, which was examined in 16 studies.

A pooled analysis of data revealed an ORR of 47.1% with both triplet and doublet pomalidomide-containing regimens. In separate analyses, the ORR of the pomalidomide plus low-dose dexamethasone doublet regimen was 35.7% vs. 61.9% with triplet regimens.

The triplet combinations with the highest ORR included pomalidomide and low-dose dexamethasone plus bortezomib (ORR = 83.5%) or carfilzomib (ORR = 77.1%), followed by:

- pomalidomide and low-dose dexamethasone plus bendamustine (ORR = 74.2%);
- pomalidomide and dexamethasone plus daratumumab (Darzalex, Janssen Oncology; ORR = 64.5%);
- pomalidomide and low-dose dexamethasone plus cyclophosphamide (ORR = 59.4%); and
- pomalidomide and low-dose dexamethasone plus doxorubicin (ORR = 32%).

Pomalidomide had an "acceptable safety profile," according to the researchers. The most common treatment-emergent adverse event was myelosuppression. Grade 3 or higher hematologic adverse events included neutropenia (47.6%), anemia (26.5%) and thrombocytopenia (20.8%). Non-hematologic adverse events included infections (29.1%), pneumonia (13.8%) and fatigue (10%).

"Our study provides useful insight into relative efficacy of various pomalidomide regimens for the treatment of [relapsed or refractory multiple myeloma] patients."

ADEELA MUSHTAQ, MD

"Moving forward, pomalidomide should be tested in combination with other agents like newer immunotherapies, monoclonal antibodies and potentially in combination with cellular therapies against multiple myeloma," Mushtaq told *HemOnc Today*. "As this drug works well in relapsed and refractory setting, it can also work for newly diagnosed, high-risk patients, and needs to be tested in prospective randomized clinical trials."

– by Stephanie Viguers ■

Reference:
Mushtaq A, et al. Abstract 2022. Presented at: ASH Annual Meeting and Exposition; Dec. 1-4, 2018; San Diego.

Disclosure: The researchers report no relevant financial disclosures.

Originally published on Healio.com/HemOnc | December 13, 2018

Daratumumab regimen yields durable responses in relapsed, refractory disease

The addition of daratumumab to lenalidomide and dexamethasone continued to demonstrate encouraging PFS rates at 3 years in patients with relapsed or refractory multiple myeloma, according to results of the multicenter, randomized, open-label, active-controlled, phase 3 POLLUX study.

Nizar Bahlis, MD, associate professor at University of Calgary in Alberta, Canada, presented updated findings from the study, which compared the outcomes of 569 patients (median age, 65 years) with relapsed or refractory multiple myeloma treated with daratumumab (Darzalex, Janssen Oncology) plus lenalidomide (Revlimid, Celgene) and dexamethasone (n = 286) with those treated with lenalidomide and dexamethasone alone (n = 283).

Nizar Bahlis

Patients received 16 mg/kg of IV daratumumab — a human monoclonal antibody that targets CD38 — every week in cycles 1 to 2, every 2 weeks in cycles 3 to 6, and every 4 weeks until progressive disease. In both groups, patients received 25 mg of oral lenalidomide on days 1 to 21 of each cycle with 40 mg of oral dexamethasone every week until progressive disease.

Previous study results — after a median follow-up of 13.5 months — showed the addition of daratumumab to lenalidomide and dexamethasone reduced the risk for progression by 63% and increased the overall response rate (93% vs. 76%; $P < .001$), complete response rate (43% vs. 19%; $P < .001$) and very good partial response rate (76% vs. 44%; $P < .001$).

Based on these data and others, the FDA approved daratumumab for use as monotherapy or in combination with lenalidomide and dexamethasone, or with bortezomib

Daratumumab *continues on page 7*

PERSPECTIVE

Edward N. Libby

Lenalidomide and dexamethasone previously were the gold standard for relapsed and refractory multiple myeloma, but the POLLUX trial changed the standard of practice with the addition of daratumumab. The original POLLUX study showed a 93% vs. a 76% ORR.

This 3-year follow-up gives us insight into how patients have done in the long-term. We see very impressive response rates. One of the things that stands out for me is the depth of response in the categories we care about, like very good partial response or better and complete response or better. In those categories, the depth of response essentially doubles compared with lenalidomide and dexamethasone. Those are dramatic and eye-catching numbers, with high statistical significance.

Another interesting addition to the study was a new category of sustained MRD negativity. This concept was applied in other myeloma trials at ASH this year. The question is whether a treatment can sustain MRD negativity for months or years.

Researchers reported a major improvement in 36-month PFS, with median PFS of 30 months vs. 20 months for the high-risk patients, an important part of this trial. In this study, MRD negative was defined as less than 10-5 presence of multiple myeloma. The patients who achieved a complete remission with MRD negativity had continued MRD testing at several time points afterward.

I think we are heading more and more in that direction in the multiple myeloma world. There was a small, but important, high-risk category within these 569 patients. Although these 65 high-risk patients were spread in both arms — which is not a huge group — they are still informative.

In terms of long-term side effects, there were no new safety signals among patients on the daratumumab regimen with 3 years of follow-up. This is a very comforting result. We know daratumumab is well tolerated in addition to being efficacious.

For me, the take-home is that at 3 years out, we continue to see a major benefit of the daratumumab/lenalidomide/dexamethasone triplet vs. lenalidomide and dexamethasone. Very significant differences were seen in the depth of response between the two regimens, and these responses were sustained.

The new benchmark of sustained MRD negativity could become a standard measurement in future trials.

Daratumumab is a game-changer and a difference-maker. In the search for the best outcomes for our patients, we can expect to see more trials of this agent in combination with all the standard backbone therapies for multiple myeloma.

Edward N. Libby, MD
Seattle Cancer Care Alliance

Disclosure: Libby reports receiving research funding from Janssen.

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Ixazomib maintenance after transplant extends PFS in newly diagnosed patients

Maintenance therapy with ixazomib significantly extended PFS compared with placebo among patients with newly diagnosed multiple myeloma who underwent autologous stem cell transplantation, according to results of the phase 3 Tourmaline-MM3 trial.

Maintenance with ixazomib (Ninlaro, Takeda) appeared to be associated with deeper responses and increased conversions to minimal residual disease negativity. The regimen also exhibited a favorable safety profile.

The findings support ixazomib as "a valuable option for maintenance therapy" for patients on response after autologous stem cell transplant, **Meletios A. Dimopoulos, MD,** chairman of the department of clinical therapeutics at National and Kapodistrian University of Athens School of Medicine, and colleagues wrote.

Meletios A. Dimopoulos

The potential of maintenance therapy to prolong disease control and extend survival after autologous stem cell transplant has been studied extensively. Lenalidomide (Revlimid, Celgene) is the only agent approved for this indication; however, lenalidomide maintenance has been associated with development of second primary malignancies, and tolerability issues also have emerged, according to study background.

Proteasome inhibitors such as bortezomib (Velcade, Takeda) are a standard backbone of myeloma treatment, and bortezomib-based maintenance regimens have demonstrated promising activity among patients who underwent autologous stem cell transplant.

However, no phase 3 trial has demonstrated a benefit of proteasome inhibitor-based maintenance compared with placebo. In addition, the clinical utility of maintenance bortezomib may be limited due to the need for regular parenteral administration and tolerability concerns, Dimopoulos and colleagues wrote.

"There is a need for an oral proteasome inhibitor maintenance therapy that can be administered for a prolonged period, improve depth of response without cumulative or late-onset toxicity, and improve convenience for patients," Dimopoulos and colleagues wrote.

The double-blind, placebo-controlled Tourmaline-MM3 study compared weekly ixazomib maintenance with placebo among patients with newly diagnosed multiple myeloma.

The study included 656 patients (median age, 57 years; range, 24-73) who achieved at least a partial response to induction therapy with a proteasome inhibitor and/or an immunomodulatory drug followed by single autologous stem cell transplant. Eighteen percent of patients had high-risk cytogenetics, such as 17p deletion, t(4;14) translocation or t(14;16) translocation.

Researchers randomly assigned patients 3:2 to ixazomib (n = 395) or placebo (n = 261) on days 1, 8 and 15 of each 28-day cycle. Ixazomib was dosed at 3 mg during the first four cycles and, if tolerated, was increased to 4 mg starting in the fifth cycle.

Treatment continued for up to 2 years, or until disease progression or unacceptable toxicity.

Investigators stratified randomization by induction regimen — proteasome inhibitor without immunomodulatory drug (59%), immunomodulatory drug without proteasome inhibitor (11%), or both (30%) — as well as preinduction International Staging System stage (37% stage I vs. 63% stage II or stage III), and response after autologous stem cell transplant (34% complete response, 45% very good partial response and 21% partial response).

Patients who underwent tandem autologous stem cell transplant or received consolidation after autologous stem cell transplant were excluded.

PFS assessed by independent review committee served as the primary endpoint. OS served as a key secondary endpoint.

Median follow-up was 31 months.

Patients assigned ixazomib achieved significantly longer median PFS (26.5 months vs. 21.3 months; HR = 0.72; 95% CI, 0.58-0.89). A landmark analysis from the time of autologous stem cell transplant also showed a significant PFS benefit for ixazomib-treated patients (median, 30.7 months vs. 24.9 months; HR = 0.68; 95% CI, 0.55-0.84).

Researchers observed the PFS benefit across subgroups, including those with International Scoring System stage III disease (HR = 0.66), proteasome inhibitor-exposed patients (HR = 0.75), proteasome inhibitor-naive patients (HR = 0.49) and those with high-risk cytogenetics (HR = 0.62).

Median OS had not been reached in either treatment group.

Results showed ixazomib was associated with a significantly higher rate of deepened response (relative risk = 1.41; 95% CI, 1.1-1.8), as well as a higher rate of conversion from documented minimal residual disease positivity at study entry to minimal residual disease negativity (12% vs. 7%).

A similar percentage of patients assigned ixazomib and placebo discontinued treatment due to adverse events (7% vs. 5%).

A higher percentage of ixazomib-treated patients experienced grade 3 or higher adverse events (42% vs. 26%) or serious adverse events (27% vs. 20%). One patient assigned ixazomib died on treatment compared with none who were assigned placebo.

The most common grade 3 or higher adverse events that occurred at greater frequency in the ixazomib group included infections (15% vs. 8%), gastrointestinal disorders (6% vs. 1%), neutropenia (5% vs. 3%) and thrombocytopenia (5% vs. < 1%).

Rates of peripheral neuropathy (19% vs. 15%) and second primary malignancies (3% each) were similar between the ixazomib and placebo groups, as were quality of life scores as assessed by the EORTC QLQ-C30 questionnaire.
– by Mark Leiser ■

Reference:
Dimopoulos MA, et al. Abstract 301. Presented at: ASH Annual Meeting and Exposition; Dec. 1-4, 2018; San Diego.

Disclosures: Dimopoulos reports receiving honoraria from Amgen, Bristol-Myers Squibb, Celgene, Janssen and Takeda.

Daratumumab

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and dexamethasone, for patients with released or refractory multiple myeloma.

The current analysis — conducted after a median 44.3 months of follow-up — includes updated 3-year data on sustained minimal residual disease (MRD) negativity and safety.

Results showed significantly longer median PFS in the daratumumab group than the lenalidomide/dexamethasone group (44.5 months vs. 17.5 months; HR = 0.44; 95% CI, 0.33-0.55).

Daratumumab also significantly prolonged PFS among patients with one previous line of treatment (HR = 0.42; 95% CI, 0.3-0.58), and across both high-risk (HR = 0.54; 95% CI, 0.32-0.91) and standard-risk (HR = 0.41; 95% CI, 0.31-0.55) cytogenetic status patients.

Using a sensitivity threshold of 10^{-5}, researchers determined that 30% of patients in the daratumumab group and 5% of those in the non-daratumumab group reached MRD negativity ($P < .000001$).

Among the intent-to-treat population, sustained MRD negativity occurred among 16% of patients in the daratumumab group and just 0.7% of those in the dexamethasone/lenalidomide group ($P < .0001$) at the 6-month or later cutoff point. By the 12-month or later cutoff, those rates were 13% with daratumumab and 0.4% without daratumumab ($P < .0001$).

Daratumumab was associated with an ORR of 93%, compared with 76% for the lenalidomide and dexamethasone alone ($P < .0001$). Similarly, the very good partial response (80% vs. 49%) and complete response rates (57% vs. 23%) significantly favored the daratumumab group ($P < .0001$ for both).

Safety data showed that grade 3 or 4 neutropenia occurred among 56% of patients in the daratumumab group and 42% of those in the dexamethasone/lenalidomide group. Grade 3 or 4 anemia and thrombocytopenia rates were comparable between the two groups, each ranging from 15% to 21%.

The discontinuation rate due to treatment-emergent adverse events was 15% in both groups. Second primary malignancies also occurred at the same rate (9%) in the groups, according to the findings.

The researchers concluded that after more than 3 years of follow-up, daratumumab with lenalidomide and dexamethasone continued to provide PFS improvements and deep responses in this patient population. Moreover, the regimen showed no negative impact on outcomes of subsequent treatment regimens, with no new safety signals.

"These updated data continue to support the use of [daratumumab plus lenalidomide and dexamethasone] in patients with relapsed or refractory multiple myeloma after first relapse," the researchers wrote.
– by Rob Volansky ■

Reference:
Bahlis NJ, et al. Abstract 1996. Presented at: ASH Annual Meeting and Exposition; Dec. 1-4, 2018; San Diego.

Disclosures: Bahlis reports honoraria and research funding from, or consultant roles with, Amgen, Celgene and Janssen. Please see the abstract for all other authors' relevant financial disclosures.

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Bisphosphonates underused among older patients with myeloma

Only about half of Medicare beneficiaries with myeloma received recommended treatment with bone-modifying agents, according to results of a population study.

Patients who used bone-modifying agents — such as zoledronate, pamidronate or denosumab (Prolia/Xgeva, Amgen) — demonstrated a reduced risk for skeletal-related events and improved OS.

"Our motivation [for conducting this research] came from our prior research in multiple myeloma, in which we observed variation in the use of myeloma therapy according to insurance-related factors," **Adam J. Olszewski, MD,** assistant professor at Alpert Medical School of Brown University, told *HemOnc Today*. "We were interested to see if parenteral bone-modifying agent use may differ according to nonclinical factors and various types of therapy (sometimes all oral), and if we could reproduce the results of a clinical trial in the population setting."

Guidelines from the International Myeloma Working Group and ASCO recommend use of bone-modifying agents for all patients initiating therapy for myeloma. Trials have shown these agents reduced the risk for skeletal-related events and are associated with improved OS.

Because adherence to these recommendations in clinical practice was unknown, Olszewski and colleagues examined the use of bone-modifying agents among Medicare beneficiaries with myeloma using the SEER-Medicare database.

The analysis included 4,670 patients (median age, 76 years; 50% women) diagnosed with myeloma between 2007 and 2013. All patients had complete Medicare claims and received outpatient chemotherapy.

Median follow-up from the start of chemotherapy was 4.6 years.

Fifty-one percent of patients received a bone-modifying agent within 90 days of starting chemotherapy. Among them, 83% received zoledronate, 16% received pamidronate and 1% received denosumab.

"This number is somewhat staggering," Olszewski said during his presentation. "This is a subgroup of patients who are older with comorbidities, and yet they were selected for active anti-myeloma therapy. There are really few contraindications for bisphosphonates, especially now that denosumab is available."

The median number of doses of a bone-modifying agent was five (interquartile range [IQR], 3-6) within 6 months, and nine (IQR, 5-11) within 12 months from chemotherapy initiation, indicating the intent for monthly treatment, Olszewski said.

Results of a multivariable analysis showed that, compared with patients aged younger than 70 years, omission of bone-modifying agents was significantly more likely among those aged 80 to 84 years (RR = 1.11; 95% CI, 1.01-1.23) and 85 years or older (RR = 1.16; 95% CI, 1.05-1.29).

Patients with a higher number of comorbidities also were less likely to receive a bone-modifying agent. For instance, omission of bone-modifying agents was 17% (RR = 1.17; 95% CI, 1.07-1.28) more likely among those with chronic kidney disease, 13% (RR = 1.13; 95% CI, 1.06-1.21) more likely among those with anemia and 29% (RR = 1.29; 95% CI, 1.15-1.45) more likely among those with end-stage renal disease.

Omission was significantly less likely among patients with a prior skeletal-related event (RR = 0.7; 95% CI, 0.62-0.79) — defined as axial or extremity fracture, or cord compression — those with hypercalcemia (RR = 0.75; 95% CI, 0.66-0.85) and those who underwent radiation (RR = 0.7; 95% CI, 0.61-0.81).

Omission also was less likely among patients who received bortezomib with an immunomodulatory antimyeloma drug compared with other treatment regimens (RR = 0.84; 95% CI, 0.74-0.94).

One possibility as to why researchers observed this low compliance rate is that "either clinicians or patients are reluctant to administer IV therapy, which comes with an additional burden of visits and injections, whereas most of antimyeloma therapy is delivered as oral or subcutaneous drugs," Olszewski told *HemOnc Today.* "However, data presented at ASH this year suggest that a pharmacist intervention may improve the rates of bone-modifying agent delivery, so perhaps the benefit of this supportive therapy seen in trials needs ongoing emphasis for clinicians and patients alike."

In total, 729 patients experienced a skeletal-related event, for a cumulative incidence function (CIF) of 13.6% (95% CI, 12.2-15). Estimated 3-year CIF of a skeletal-related event was 11.2% among patients who received a bone-modifying agent and 14.1% among those who did not.

Patients who received a bone-modifying agent demonstrated a significantly reduced risk for a skeletal-related event in the entire cohort (subhazard ratio [SHR] = 0.83; 95% CI, 0.7-0.98) and in a propensity score-matched subcohort of 3,152 patients (SHR = 0.78; 95% CI, 0.64-0.94).

Median OS was 3.1 years (95% CI, 2.9-3.2) in the total cohort.

Patients who received a bone-modifying agent experienced improved OS (adjusted HR = 0.84; 95% CI, 0.77-0.92), but survival did not significantly differ according to type of agent.

"This effect has been observed in randomized trials, so it likely indicates primary antimyeloma activity — possibly through bone microenvironment — or the effect on patients' skeletal health, as fractures and other skeletal-related events have a significant impact on patients' functional status, and possibly the overall clinical course," Olszewski told *HemOnc Today*. "Of course, our study is observational, so it is possible that there were unobserved differences between groups responsible for the survival difference."

Research should focus on understanding barriers to the appropriate use of supportive care in myeloma and interventions to improve compliance with guidelines, Olszewski said.

"It will be also interesting to see in the future if the wider availability of denosumab — with its approval in myeloma in 2018 — might provide an option for patients who were not eligible or opted out of treatment with intravenous bisphosphonates," he added. – *by Alexandra Todak* ■

Reference:
Olszewski AJ, et al. Abstract 709. Presented at: ASH Annual Meeting and Exposition; Dec. 1-4, 2018.

Disclosure: Olszewski reports research funding from Genentech, Spectrum Pharmaceuticals and TG Therapeutics, and a consultant role with Spectrum Pharmaceuticals.

PERSPECTIVE

Jason Valent

ASCO and International Myeloma Working Group guidelines state to use a bone-modifying agent — whether it's zoledronic acid, pamidronate or denosumab — monthly for at least 2 years for the bisphosphonates, and then to consider extending that treatment depending on the status of the patient's disease. In theory, all patients diagnosed with myeloma should be placed on a bone-modifying agent.

It would have been interesting if this paper could have evaluated patients who specifically had bone disease identified by imaging at diagnosis. For patients without identifiable bone disease at diagnosis, there may not be as much benefit to bone-modifying agents. Do those patients really need a bone-modifying agent? The answer according to the guidelines is yes. But you may not prevent as many skeletal-related events in someone who doesn't have identifiable bone disease. This may have financial impacts in a Medicare system.

The proportion of patients who received a bisphosphonate in this analysis was stunning in a bad way; 51% is awful. I couldn't hypothesize a good rationale as to why the number would be so high. If 15% to 20% of patients were not receiving a bisphosphonate, you could argue that those were the patients who did not have bone disease at diagnosis. As a myeloma doctor, it may be easier for us to include the bone-modifying agent as we do this every day. I am sure that there are some patients that we miss, but usually that is resolved by month 2 of therapy.

Another thing that is very interesting about this study is the absolute difference in skeletal-related events — 14% with nontreatment vs. 11% with a bisphosphonate. From a Medicare standpoint, those data indicate the number needed to treat is 35 to prevent one skeletal-related event. From a cost-effective standpoint, that's not ideal. This is where it may have helped to just analyze patients who had identifiable bone disease, but perhaps it was hard to pick them out of the data. I would expect a larger difference between treatment and nontreatment groups if you were just looking at the group with identifiable bone disease. This may reduce the number needed to treat.

We've been looking at use of bone-modifying agents at our own institution as a quality measure. We have found that doctors are very good about explaining the chemotherapy, and we don't focus as much on supportive care. In theory, bone-modifying agents should not be considered supportive care, they should be considered part of the patient's therapy. We had not prioritized bone-modifying agents like we should be, similar to what is seen in this study. Thus, one of the big explanations is that people just don't prioritize it the same way they do chemotherapeutics. This is what I speculate would be the cause of a 49% nonuse rate. Another approach to improve compliance would be to use the electronic health record. If you enter a diagnosis of multiple myeloma, you can build in a stop that you cannot close the record until you put in the order for a bisphosphonate. That would be a safeguard you could build in from an institutional standpoint to make sure you aren't missing this.

Jason Valent, MD
Taussig Cancer Institute
Cleveland Clinic

Disclosures: Valent reports no relevant financial disclosures.

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Addition of daratumumab decreases multiple myeloma progression, mortality risk

The addition of daratumumab to lenalidomide and dexamethasone reduced the risk for disease progression or death by 45% among patients with transplant-ineligible, newly diagnosed multiple myeloma, according to results of a phase 3 randomized trial.

The safety profile of the combination regimen was consistent with previous studies of daratumumab (Darzalex; Janssen, Genmab), a human monoclonal antibody that targets CD38, according to researchers.

"We believe this study has established [the addition of daratumumab to lenalidomide and dexamethasone] as a new standard of care for patients who are ineligible for autologous stem cell transplantation," **Thierry Facon, MD,** professor of hematology at Lille University Hospital in Lille, France, said during a presentation.

Previous phase 3 studies showed that adding daratumumab to the standard of care for patients with relapsed or refractory multiple myeloma (bortezomib [Velcade, Takeda] and dexamethasone) and transplant-ineligible, newly diagnosed multiple myeloma (bortezomib, melphalan and prednisone) reduced the risk for disease progression or death by 50% or more.

The global study by Facon and colleagues included 737 patients (median age, 73 years; range, 45-90; 52% men) from 14 countries who were ineligible for high-dose chemotherapy with autologous stem cell transplantation due to age or comorbidities. The researchers randomly assigned patients to 16 mg/kg of IV daratumumab (once a week for cycles 1-2, once every 2 weeks for cycles 3-6, and once every 4 weeks thereafter) with 25 mg of lenalidomide (Revlimid, Celgene) on days 1 to 21 and 40 mg of dexamethasone on days 1, 8, 15 and 22 (n = 368), or lenalidomide and dexamethasone alone (n = 369). Stratification was based on International Staging System stage, region (North America vs. other) and age.

All patients received 28-day cycles of lenalidomide and dexamethasone with or without daratumumab until disease progression or unacceptable toxicity. PFS served as the study's primary endpoint. The secondary endpoints were overall response rate, minimal residual disease negativity rate and safety.

"This is a gentle regimen for elderly or very elderly [patients]."

THIERRY FACON, MD

The researchers performed the prespecified interim analysis after 238 PFS events and a median follow-up of 28 months. They observed a 45% reduction in the risk for disease progression or death among patients who received daratumumab (HR = 0.55; 95% CI, 0.43-0.72). Median PFS for patients who received lenalidomide and dexamethasone was 31.9 months and was not yet reached in the daratumumab group.

Facon reported that 19% of the patients had died. The HR for OS was 0.78 (95% CI, 0.56-1.1).

Adding daratumumab to the combination of lenalidomide and dexamethasone resulted in complete response or better rate of 47.6% compared with 24.7% in the lenalidomide and dexamethasone group (OR = 2.75, 95% CI, 2.01-3.76). The very good partial response or better rate was 79.3% in the daratumumab group compared with 53.1% in the lenalidomide and dexamethasone group (OR = 3.4, 95% CI, 2.45-4.72).

A greater proportion of patients assigned to daratumumab achieved minimal residual disease negativity (24% vs. 7%; $P < .0001$). Higher rates of grade 3 or 4 pneumonia (14% vs. 8%) and neutropenia (50% vs. 35%) were observed in the daratumumab group. Fatal treatment-related adverse events occurred in 7% of patients in the daratumumab group and 6% in the control group.

"As you can see, the PFS for [the addition of daratumumab to lenalidomide and dexamethasone] is very high," Facon said. "The benefit we have in this study is the benefits for patients over the age of 75 years. This is a gentle regimen for elderly or very elderly [patients]." – *by John DeRosier* ■

Reference:
Facon T, et al. Abstract LBA-2. Presented at: ASH Annual Meeting and Exposition; Dec. 1-4, 2018; San Diego.

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