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Daratumumab Added to Lenalidomide and Dexamethasone Extends Survival in Transplant-Ineligible Patients With Newly Diagnosed Multiple Myeloma

By Laurie Saloman, MS

CERTAIN PATIENTS WITH multiple myeloma, typically older ones, are poor candidates for stem cell transplant and must rely on alternative treatments.¹ Daratumumab, a human, CD38-targeting, immunoglobulin G kappa, is an approved monotherapy treatment for people who have relapsed/refractory multiple myeloma (RRMM). It also is approved to be used with standard-of-care therapy for patients with RRMM or newly diagnosed multiple myeloma (NDMM).¹

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Enhancer Hijacking of *BCL11B* Defines an Acute Leukemia Subtype

By Brian Dunleavy, MA

SOME CASES OF acute leukemias of ambiguous lineage (ALAL) have a distinct genetic profile, including T-lymphoid/myeloid mixed phenotype acute leukemia (MPAL), early T-cell precursor acute lymphoblastic leukemia (ETP-ALL), and acute myeloid leukemia (AML), according to study results presented during the 62nd American Society of Hematology Annual Meeting and Exposition.

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Daratumumab Added to Lenalidomide and Dexamethasone Extends Survival in Transplant-Ineligible Patients With Newly Diagnosed Multiple Myeloma

(CONTINUED FROM COVER)

A phase 3 study has demonstrated that adding daratumumab to standard-of-care therapeutic regimens enables longer progression-free survival (PFS) and increased levels of minimal residual disease (MRD) negativity.

A multinational team conducted an analysis of the outcomes of daratumumab plus lenalidomide and dexamethasone (D-Rd) compared with lenalidomide and dexamethasone (Rd). Shaji K. Kumar, MD, an investigator and consultant in the Division of Hematology at Mayo Clinic in Rochester, Minnesota, led an analysis examining data from the phase 3 MAIA study (NCT02252172), which involved 737 patients with NDMM who were ineligible for high-dose chemotherapy and autologous stem cell transplantation because they were at least 65 years old or had comorbidities. Kumar presented the results of this analysis at the 62nd American Society of Hematology Annual Meeting and Exposition. Participants in the analysis ranged in age from 45 to 90 years old, with a median age of 73 in the D-Rd arm and 74 in the Rd arm. Forty-four percent of participants were at least 75 years old. Twenty-seven percent of patients were International Staging System (ISS) stage I, 43% were ISS stage II, and 29% were ISS stage III. Of the 642 patients for whom information was available, 14% had high cytogenetic risk and 86% had standard risk.¹

Participants were randomized in a 1:1 ratio to receive either a D-Rd regimen or an Rd regimen. All patients were on 28-day medication cycles. The primary end point was progression-free survival. Secondary end points included overall response rate and MRD-negativity rate.

In the Rd arm, the medication regimen consisted of 25 mg of lenalidomide once a day for the first 3 weeks and 40 mg of dexamethasone on days 1, 8, 15, and 22. Patients in the D-Rd arm received the same regimen, plus 16 mg of daratumumab once a week during the first 2 cycles, once every 2 weeks during the third through sixth cycles, and then every 4 weeks afterward. Treatment was maintained until there was disease progression or the emergence of toxic adverse events (AEs) that made continuation unacceptable.

“In the primary analysis of the phase 3 MAIA study [with] a median follow-up of 28 months, a progression-free survival benefit and a greater than 3-fold increase in MRD-negativity rates were observed with D-Rd versus Rd in patients with transplant-ineligible newly diagnosed multiple myeloma,” Kumar said. “With a longer median follow-up of 36.4 months, D-Rd was shown to be maintaining a progression-free survival benefit and continued to demonstrate improved rates of deep and durable responses as compared [with] lenalidomide/dexamethasone alone.”

The outcome curves in the 2 groups continued to diverge as the study went on; participants receiving D-Rd lived progressively longer with no worsening of their disease. At a median follow-up of 48 months, 60% of



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participants in the D-Rd arm had experienced PFS versus 38% in the Rd arm.

“D-Rd demonstrated a benefit in progression-free survival, with a 46% reduction in the risk of disease progression or death versus Rd alone,” Kumar said. This benefit generally was consistent across all patient subgroups, including those who had high cytogenetic risk.

In addition, the MRD-negativity rate in the D-Rd group was 31% at 48 months versus 10% in the Rd group, with sustained MRD-negativity rates of 20% in the D-Rd group versus 5% in the Rd group after at least 6 months and 16% in the D-Rd group versus 3% in the Rd group after at least 12 months.¹

The median duration of the study was 42.8 months for those in the D-Rd arm and 22.6 months for those in the Rd arm, with 48.4% of patients in the D-Rd arm and 74.8% in the Rd arm discontinuing study treatment.

“The longer duration of therapy in [the D-Rd] arm reflects the decreased risk of progression associated with the use of 3 drugs compared with 2 drugs,” Kumar noted. “Patients were not allowed to cross over to the other arm based on suboptimal response or disease progression. If they had disease progression, they would go off trial, and then they would be able to get treated on drugs that are available outside of clinical trials or potentially enroll in other trials that are designed for relapsed myeloma.”

A longer follow-up period (median 48 months) demonstrated an improvement in PFS on the next line of therapy (PFS2), specifically for patients in the D-Rd arm of the trial. D-Rd participants were recorded as not having reached the next line of therapy, whereas Rd participants reached it in 51.3 months.

Grade 3 to 4 AEs that emerged during treatment include neutropenia (experienced by 53% of those on D-Rd versus

37% of those on Rd) pneumonia (18% vs 11%), anemia (16% vs 21%), lymphopenia (16% vs 11%), hypokalemia (12% vs 10%), leukopenia (11% vs 6%), and cataract (11% vs 10%). Treatment-emergent AEs led 11% of those in the D-Rd arm and 22% of those in the Rd arm to discontinue treatment.

“In this phase 3 trial, we found that addition of daratumumab improves the depth of response[s] as well as the frequency of responses,” Kumar said. “It also improved the progression-free survival, which reflects better disease control. The updated analysis demonstrates an impact of daratumumab on patients with high-risk genetic abnormalities, which was not evident at the initial analysis. In addition, it also shows improvement in PFS2, which is commonly considered a surrogate marker for overall survival.”

Kumar noted that although daratumumab’s dosing schedule is frequent during the first 8 weeks of use, it becomes less burdensome afterward as doses are more spaced out. Daratumumab now can also be given as a subcutaneous injection, making it easier to administer. ♦

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Enhancer Hijacking of BCL11B Defines an Acute Leukemia Subtype

(CONTINUED FROM COVER)

Using high-throughput sequencing, investigators observed structural alterations in the *BCL11B* transcription factor gene among the samples studied. These structural alterations put *BCL11B* under the transcriptional control of powerful enhancers, a process that investigators described as “enhancer hijacking”—active in normal stem and progenitor cells, causing aberrant expression of the gene.

Ultimately, the findings could change the way leukemia subtypes are classified and treated, they said.

“We showed how transcriptional analysis of diverse leukemia samples can identify biologically similar leukemia subtypes that will be missed using conventional immunophenotype-based approaches,” Lindsey Montefiori, PhD, a postdoctoral fellow at St Jude Children’s Research Hospital in Memphis, Tennessee, said during the presentation. “Specifically, using this approach we identified a subtype of lineage-ambiguous acute leukemias [composed] of multiple diagnostic entities that shared a

highly distinct gene expression profile. All of these samples harbored genomic rearrangements that resulted in *BCL11B* deregulation, which encodes a transcription factor that is normally active only in T lineage cells. This finding represents an important first step in understanding the mechanism of leukemogenesis and the lineage [aberrant] characteristic of these leukemias.”

ALALs, including those that express combinations of myeloid, T-cell lineage, and stem cell markers such as MPAL and ETP-ALL, pose a clinical challenge because they are difficult to diagnose, classify, and treat, according to Montefiori and colleagues.¹

To define the genomic basis of these leukemias, they performed a large pan-acute analysis of 2573 samples, including 774 T-cell ALL (T-ALL), 126 MPAL, 262 AML, and 1411 B-cell ALL cases, using transcriptome and, in some cases, whole genome sequencing. T-distributed stochastic neighbor embedding and hierarchical clustering analyses of RNA-sequencing data revealed a new subtype of 60 samples with a distinct gene expression profile and immunophenotype (cCD3+ CD7+ CD1a- CD2+ CD5- CD8- cMPO+/- and myeloid/stem cell marker positive). Among the 55 cases for which they had data, 25 (45.5%) were T-lymphoid/myeloid MPAL, 20 (36.4%) ETP-ALL, 8 (14.5%) AML, and 2 (3.6%) undifferentiated leukemia. Overall, 44 (80%) cases harbored *FLT3* gene alterations.

Notably, these 44 cases exhibited monoallelic expression of *BCL11B*, which encodes a T-lineage transcription factor that is repressed in hematopoietic stem and progenitor cells, “a putative cell of origin for ALAL,” the researchers noted. Whole genome and RNA sequencing identified recurrent *BCL11B*-deregulating structural variants in 56 of 60 (93.3%) cases, they said. These included *BCL11B* fusion to *RUNX1* or *ZEB2* in 6 (10%) cases.

Most of these structural variants were noncoding and included rearrangement of *BCL11B* to a gene desert upstream of *ARID1B* on chromosome 6 in 23 cases (41%); rearrangement to the BENC enhancer at *CCDC26*, distal to *MYC* on chromosome 8 in 9 cases (16%); rearrangement to an intronic region of *CDK6* on chromosome 7 in 4 cases (7%); a novel high-copy (approximately 20-fold) tandem amplification of a 2.5-kilobase (kb) noncoding region 700 kb downstream of *BCL11B* on chromosome 14, which investigators called *BCL11B* enhancer tandem amplification (BETA; 12 cases/21%); and rearrangement to noncoding regions at the *SATB1* and *ETV6* loci (each observed in a single case). Interestingly, they noted, *BCL11B*-deregulating structural variants were not identified in whole genome sequencing of 5550 pediatric and adult hematological malignancies, 344 pediatric brain tumors, and 797 pediatric solid tumors.

The investigators concluded that these structural variants cause enhancer hijacking and ectopic activation of *BCL11B* in a CD34+ hematopoietic stem and progenitor cell. They found that *ARID1B*, *CCDC26*, *CDK6*, and *ETV6* loci all harbor CD34+ superenhancers, which are absent (*ARID1B*, *CCDC26*, *ETV6*) or diminished (*CDK6*) in committed T-cell precursors. Although the BETA region is nominally active in hematopoietic stem and progenitor cells, tandem amplification generates an approximately 50-kb chromatin domain that “may transform this region into a potent transcriptional activator,” they said.

By investigating this using H3K27Ac chromatin conformation capture and high-throughput sequencing on 5 primary samples (1 *ARID1B*, 1 *CCDC26*, 1 *CDK6*, and 2 BETA), normal cord blood CD34+ cells, and 2 T-ALL cell lines, they confirmed that the rearranged CD34+ enhancers are active and interact with *BCL11B*, which supports the enhancer hijacking mechanism. In addition to looping to *BCL11B*, BETA also activates the T-cell-specific ThymoD enhancer 1 Mb distal of *BCL11B*, they said.

This tandem amplification of “a short, inconspicuous noncoding region generates a powerful de novo enhancer,” ectopically activating *BCL11B* 700 kb downstream and co-opting a dormant T-cell enhancer 300 kb in the opposite direction—activations that, in turn, “likely collaborate to drive oncogenic *BCL11B* expression” in hematopoietic stem and progenitor cells, the investigators added.

“We think our findings provide support for eventually integrating transcriptional profiling as a diagnostic tool,” Montefiori said. “It is clear that flow cytometry-based approaches are not always able to accurately distinguish biologically distinct leukemias, and as diagnosis directly plays into therapy, we believe it will be important to incorporate orthogonal approaches to characterizing individual leukemia samples in the future. We acknowledge this is not currently feasible, as it requires next-generation sequencing and does not have a rapid turnaround time. Additionally, we are still in a discovery phase in terms of identifying and cataloging diagnostically relevant gene expression signatures [and] understanding the relationship between these signatures and leukemia biology, response to treatment, and outcome. Despite this, we are optimistic that these challenges will be overcome in the near future to enable a more comprehensive assessment of leukemia subtypes.” ♦

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Study Results Reveal Outcomes of Maintenance Therapy After Autologous Stem Cell Transplant in Newly Diagnosed Multiple Myeloma

By Laurie Saloman, MS

RANDOMIZED CLINICAL TRIALS have demonstrated that patients with newly diagnosed multiple myeloma (NDMM) who receive frontline autologous stem cell transplantation (ASCT) achieve prolonged progression-free survival. National Comprehensive Cancer Network (NCCN) guidelines also recommend maintenance therapy for NDMM patients after ASCT. Yet there has been a lack of data on the use and outcomes of maintenance therapy in contemporary clinical practice.

The results of a new study shed light on the outcomes in NDMM patients receiving frontline ASCT followed by maintenance therapy. Conducted by Janssen Pharmaceuticals, the retrospective observational cohort study included patients who received initial diagnoses of multiple myeloma between 2011 and 2018.¹ Patient data were harvested from the Flatiron Health database, which contains deidentified longitudinal data from more than 2.4 million cancer patients at 280 cancer clinics throughout the United States. Flatiron Health's database includes not only measurable, structured data but also unstructured data such as clinician notes.

To be included in the trial, participants had to have had at least 2 clinic visits with Flatiron Health between 2011 and 2018, been in contact with Flatiron Health within 60 days after ASCT so posttransplant consolidation and maintenance therapy could be recorded, and not been part of a clinical trial or undergone a second transplant within 6 months of their initial transplant.

Participants were considered to have been on maintenance therapy if they received an NCCN-approved maintenance therapy regimen or continued taking a subset of any antimyeloma agents after undergoing ASCT and, if applicable, consolidation therapy anytime within 6 months of ASCT. NCCN guidelines for maintenance therapy for multiple myeloma include lenalidomide, bortezomib, and ixazomib.

The study looked at age, disease stage, cytogenetic risk, and the kinds of treatments patients received. Key measures of clinical outcomes included the time to next treatment and overall survival. For time to next treatment and overall survival measurements, follow-up began 90 days after ASCT or on the date maintenance therapy

began, depending on which occurred first. Data were captured through May 30, 2020, or until patients were lost to follow-up, whichever came first. The investigators used Kaplan-Meier estimators and Cox regression models to analyze treatment duration and clinical outcomes.

“In terms of the use of maintenance and consolidation therapy post transplant, we found that about 7% in the study cohort received consolidation post transplant and 74% received maintenance therapy, the most common regimen being lenalidomide monotherapy,” said Eric M. Ammann, PhD, of Janssen Scientific Affairs, Horsham, Pennsylvania, an author of the study. “Medium duration in the study cohort was 18 months, and that was fairly similar for the patients who were getting lenalidomide and bortezomib monotherapy.”

“In terms of the use of maintenance and consolidation therapy post transplant, we found that about 7% in the study cohort received consolidation post transplant and 74% received maintenance therapy, the most common regimen being lenalidomide monotherapy.”

— Eric M. Ammann, PhD
Janssen Scientific Affairs
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The use of maintenance therapy after ASCT increased during the study period. It was 69.3% from 2011 to 2013, and it then rose to 79% in 2018, likely due to FDA approval of lenalidomide as a maintenance therapy in 2017, along with clinical trial data supporting the use of maintenance therapy. Nevertheless, 26% of patients in the study never had maintenance therapy, suggesting an unmet clinical need.

There was little difference in the median ages of patients and the percentages of cytogenetic risk in those who received maintenance therapy and those who didn't. “It's notable, though, that the cytogenetic risk and what

patients received as induction therapy [were] somewhat predictive of the specific maintenance regimen that patients [received],” Ammann said.

“Both bortezomib and lenalidomide maintenance were associated with superior time to next treatment relative to no maintenance, and with respect to overall survival, lenalidomide was associated with a marginal advantage in overall survival relative to no maintenance,” Ammann said. Lenalidomide was the most commonly used maintenance drug in the United States, followed by bortezomib. Bortezomib, which had a limited sample size in this study, did not appear to bestow any meaningful benefit when it came to overall survival.

The study had several limitations, according to Ammann. The use of consolidation and maintenance therapy after

ASCT had to be inferred based on observed treatment patterns due to Flatiron Health’s lack of documentation of reasons for treatment, and all of the results were unadjusted and subject to confounding biases. The investigators asserted that additional maintenance regimens to improve clinical outcomes should be explored for this patient population. ♦

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In Early Data, Etranacogene Dezaparvovec Proves Promising in Adults With Severe or Moderate-Severe Hemophilia B

By Amber Schilling, PharmD

AFTER 54 MEN with severe or moderately severe hemophilia B were given a single IV dose of etranacogene dezaparvovec, a novel gene therapy under investigation for use in this disorder, activity of clotting factor IX (FIX) increased from baseline into the mild-to-normal range at 26 weeks.¹ This is a preliminary, interim finding of the Health Outcomes with Padua gene Evaluation in hemophilia B trial (HOPE-B; NCT03569891), a phase 3 trial assessing efficacy and safety of etranacogene dezaparvovec that is scheduled to continue for a total of 5 years.¹ The results were presented by Steve W. Pipe, MD, of University of Michigan, Ann Arbor, during the 62nd American Society of Hematology Annual Meeting and Exposition.

Hemophilia is a congenital bleeding disorder caused by a deficiency in clotting factor VIII (FVIII; hemophilia A) or in FIX (hemophilia B).² The disorder is rare, affecting predominantly males who inherit an affected maternal X chromosome that codes for a pathogenic variant of the *F8* or *F9* clotting factor gene. The estimated prevalence at birth is 24.6 and 5.0 cases per 100,000 males for hemophilia A and B, respectively.² Most cases (80%-85%) are diagnosed as hemophilia A and the remainder (15%-20%) as hemophilia B.²

Because current treatments are not curative, hemophilia is a lifelong disease characterized by spontaneous and/or prolonged hemorrhaging, musculoskeletal complications from hemarthrosis (joint bleeds), and a variety of other sequelae.² Hemophilia severity is defined according to the level of deficient clotting factor relative to normal: mild (< 40% but > 5% of normal), moderate (\leq 5% but \geq 1% of normal), and severe (< 1% of normal).^{2,3}

For the past 50 years, the primary focus for hemophilia treatment has been on clotting factor replacement therapy to both treat and prevent bleeds. According to the World Federation of Hemophilia 2020 treatment guidelines, the current standard of care remains the use of exogenous clotting factor concentrates (CFCs).² However, CFCs can be cumbersome for several reasons: (1) They have an inherently short half-life and therefore require frequent dosing, (2) they can be rendered ineffective and cause anaphylaxis if the patient develops autoantibodies (“inhibitors”) against the infused clotting factors, and (3) they are not curative and therefore must be administered over the patient’s entire lifetime to maintain hemostasis.^{2,3}

Although half-life extenders and bypassing agents have been developed to overcome some of these challenges, the

approach remains noncurative and costly, and it has been associated with reduced quality of life due to the need for lifelong injections.^{2,4,5} A gene therapy could ameliorate these challenges and be potentially curative if it could successfully induce endogenous expression of the deficient clotting factor.^{4,6} However, a key barrier to gene therapy has been selecting a virus vector for DNA transfer that does not become neutralized by the patient's own immune system, rendering it inactive for gene transfer.⁶⁻⁸

In an animal study, a nonpathogenic adeno-associated virus 5 (AAV5) vector was utilized to transfer the human genetic variant *FIX*-Padua (h*FIX*-Padua) gene into host DNA within hepatocytes.⁵ The h*FIX*-Padua variant is a hyperactive *FIX* variant that has been shown to demonstrate a 5- to 10-fold increase in *FIX* activity relative to wild-type *FIX*-Padua.⁶ AAV5-h*FIX* was injected into nonhuman primates (NHPs) at several doses, and it increased levels of circulating h*FIX* protein, ranging from 1% to 2% of normal human levels in the low-dose group to 60% in the high-dose group.⁵ Increased expression of *FIX* was maintained up to 26 weeks post treatment with a single dose.⁵ The mean increase from baseline of *FIX* activity detected was 58.9%.⁵

“The most common safety findings were transaminase elevations requiring steroid treatment and infusion-related reactions, supporting a safety profile consistent with early phase studies.”

— Steven W. Pipe, MD
University of Michigan
Ann Arbor, Michigan

Data from a small, open-label, single-dose, multicenter phase 2b dose confirmation study showed that etranacogene dezaparvovec, a gene therapy that utilizes the nonpathogenic AAV5 vector to transfer the h*FIX*-Padua gene into host DNA within hepatocytes, increased endogenous *FIX* activity in 3 patients with moderate-to-severe hemophilia B (*FIX* activity at baseline \leq 1% of normal).⁴⁻⁶ After receipt of 1 dose of the study drug (500-mL infusion of 2×10^{13} genome copies/kg [cg/kg]), endogenous mean *FIX* activity increased to means of 31% of normal at 6 weeks (individual levels of 37.8%, 23.9%, and 30.0% of normal in participants 1 through 3, respectively), 38.0% at

12 weeks (37.9%, 24.9%, and 51.1%, respectively), and 47% at 26 weeks (51.0%, 33.2%, and 57.0%, respectively).⁴

Of note, all patients in the phase 2b trial had neutralizing antibodies (NABs) to the AAV5 vector at screening, a fact previously predicted to preclude successful gene transfer. Given that the presence of preexisting anti-AAV5 NABs did not appear to interfere with AAV5-mediated gene transfer in the phase 2b study and that clinical trials investigating gene therapies have historically excluded patients who have neutralizing antibodies to the vector capsid serotype, this was a promising finding.⁴

Results of the dose-finding phase 2b trial were designed to be utilized for the HOPE-B trial, a larger, phase 3 trial of etranacogene dezaparvovec.⁴ The HOPE-B trial is an ongoing, open-label, single-dose, single-arm, multinational trial in men who have severe or moderate-severe hemophilia B that was designed to assess the safety and efficacy of etranacogene dezaparvovec at 26 weeks and 52 weeks.¹ *FIX* activity at 26 and 52 weeks was a primary efficacy end point; adverse events (AEs) were a secondary end point.

Consistent with the design and results of the phase 2b trial, as well as trials including NHPs, HOPE-B did not exclude patients with prevalent anti-AAV5 NAB titers. All 54 participants had hemophilia B (44 severe, 10 moderate-severe; 42.6% had NABs to AAV5 at baseline) and were given a single IV dose of etranacogene dezaparvovec at 2×10^{13} cg/kg. At week 26, *FIX* activity had increased to a mean of 37.2%, which represented a change from baseline of 36.0% ($P < .0001$). Most treatment-related AEs (TRAEs) reported were mild (81.5%), with headache and influenza-like illness being among the most common. Pipe noted that no serious TRAEs were recorded, and there were no deaths. Seven patients had an infusion-related reaction, and the infusion was discontinued in 1 patient; 9 patients had treatment-related elevations in liver enzymes.¹ “The most common safety findings were transaminase elevations requiring steroid treatment and infusion-related reactions, supporting a safety profile consistent with early phase studies,” said Pipe.

The animal studies in NHPs, the dose-confirmation phase 2b trial, and the preliminary results of the HOPE-B trial all point to the promise of etranacogene dezaparvovec as a novel gene therapy in patients with hemophilia B. ♦

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Investigators Examine Hematological Malignancies and Risk of COVID-19

By Laurie Saloman, MS

PATIENTS WITH HEMATOLOGICAL MALIGNANCIES (HMs) are part of a population of immunocompromised patients considered to be at high risk of contracting coronavirus disease 2019 (COVID-19). This is true even though data are lacking on the typical diagnosis, presentation, outcomes, and path of the disease in these patients. Compounding the problem is that it appears to be more difficult to accurately diagnose severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in patients who have HM than to detect the virus in the general population.¹

A study from Tulane University included patients with HM, ranging in age from 24 to 82 years. Their conditions included acute myeloid leukemia, chronic myelogenous leukemia, multiple myeloma, B-cell acute lymphoblastic leukemia, diffuse large B-cell lymphoma, classical Hodgkin lymphoma, and other lymphoid and myeloid cancers. From March 2020 to October 2020, 20 patients had been on an active chemotherapy regimen, 6 had undergone autologous stem cell transplants, 6 had undergone allogeneic transplants, and 7 were under active surveillance. Thirty-three patients had symptoms of COVID-19, and 6 patients presented as asymptomatic.

Thirty-nine patients were first tested with nasopharyngeal reverse transcription polymerase chain reaction (RT-PCR). Twenty-six tested positive and 13 tested negative. Due to clinical suspicion, 8 of the 13 negative patients were retested using clustered regularly interspaced short palindromic repeats (CRISPR) technology, with the results of 7

returning as positive. Of the 5 patients who initially tested negative and were not retested with CRISPR, 3 died, 1 was proactively treated for COVID-19 with hydroxychloroquine and azithromycin and improved, and 1 was asymptomatic.

Of the 33 total patients who tested positive by either RT-PCR or CRISPR testing, 9 underwent COVID-19–directed therapy, receiving hydroxychloroquine/azithromycin, remdesivir, and/or convalescent plasma. After being placed on these therapeutic regimens, 8 patients improved and 1 died.

CRISPR technology offers a more sensitive test than the RT-PCR tests. It works by using a short segment of DNA that reacts to a particular target; in this case, RNA from SARS-CoV-2. Positivity is expressed as a fluorescence, which is detectable and measurable.

According to Alex Niu, MD, who presented this abstract at the 2020 American Society of Hematology Annual Meeting and Exposition, clinicians have been unable to pinpoint the exact reason why it is harder to diagnose COVID-19 in patients with HM. It is possible that those who presented with milder disease experienced less viral shedding, giving a higher likelihood of a false-negative test result. These patients could have been tested during the very early stages of the disease course. It is also conceivable that they are so immunocompromised that even a small amount of virus causes severe effects. Possibly, these effects cannot be detected using the nasopharyngeal RT-PCR tests but only by using a more sensitive assay, which would include the CRISPR test.

It is believed that the altered immune system of patients with HM is likely responsible for the high mortality rate these patients experience when tested for COVID-19, a rate that was at least 20% in the study. “First, studies have shown that COVID-19 infection causes a lymphopenia, specifically a B-cell lymphopenia, so when patients are infected with COVID-19, their immune systems become impaired,” Niu said. “In addition, in patients with hematologic malignancies, these patients already have altered immune systems due to their underlying disease, as well as the treatments they’ve received, as many chemotherapy agents cause a lymphopenia, specifically a T-cell lymphopenia. Thus, those patients already start off with an inability to generate an adequate immune response.”

The study patients who had received lymphodepleting chemotherapy within 30 days of COVID-19 diagnosis had significantly worse outcomes than those who had not received the chemotherapy ($P = .039$). Overall, 12 of the 39 participants died, for a mortality rate of 32%. The Kaplan-Meier survival curve showed an approximate overall survival of roughly 65%. The study’s mortality rate was 30% to 60%, which is higher than that of the general population. Most deaths occurred within 25 days of a COVID-19 diagnosis.

Among the limitations of this study were its relatively small size and the lack of standardized testing

for COVID-19. Patients were tested with different types of nasopharyngeal RT-PCR, and not all were tested with CRISPR, which is still a relatively new entity in the diagnosing of COVID-19. Niu also pointed out that not all patients in the study were treated for COVID-19, and those who did receive treatment were not all on the same regimen.

When asked about the effects of COVID-19 on malignancy progression, Niu was confident that it has detrimental effects on patients’ well-being. Because they may be so sick with COVID-19 symptoms, patients have to delay treatment for their HM conditions, which allows the disease to progress. Also, he noted, clinicians should consider empirically treating for COVID-19 where high suspicion remains in patients who continually test negative. Results of studies have shown that earlier treatment initiation is associated with better outcomes. More research is needed on the long-term effects of COVID-19 in patients with HM. ♦

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Daratumumab-Based Regimens Produce Better Outcomes for Patients With Transplant-Ineligible, Newly Diagnosed Multiple Myeloma

By Valerie Sjoberg

RESULTS FROM PHASE 3 CLINICAL TRIALS MAIA (NCT02252172) and ALCYONE (NCT02195479) previously demonstrated that the human immunoglobulin G kappa monoclonal antibody daratumumab (DARA; D), when added to the standard-of-care regimens lenalidomide and dexamethasone (Rd) and bortezomib, melphalan, and prednisone (VMP), improves rates of minimal residual disease (MRD) negativity for patients with newly diagnosed multiple myeloma (NDMM) who are transplant ineligible.^{1,2} These higher rates are associated with longer progression-free survival (PFS).³ According to findings from MAIA, ALCYONE, and a pooled analysis of these 2 studies,

sustained MRD negativity lasting 6 months or more or 12 months or more is associated with longer PFS than that of MRD negativity lasting less than 6 months.¹⁻³

In the studies’ intention-to-treat populations, MRD negativity improved by 28.8% for patients in the D-Rd treatment arm versus 9.2% for patients in the Rd treatment arm ($P < .0001$) and 28.3% for those receiving D-VMP versus 7.0% for those receiving VMP ($P < .0001$). An MRD-negative status was associated with longer PFS than that of an MRD-positive status regardless of the treatment regimen.³

MRD is currently being explored as a measure of tumor cells in bone marrow to help identify the status of cancer

remission.^{3,4} “Recent treatment advancements for patients with NDMM have led to improved long-term outcomes,” said lead study author Jesus F. San-Miguel, MD, PhD, of Clínica Universidad de Navarra-Centro de Investigación Médica Aplicada, Instituto de Investigación Sanitaria de Navarra, Centro de Investigación Biomédica en Red de Cáncer, Pamplona, Spain. “Therefore, new ways to evaluate treatment efficacy are needed. MRD is a strong prognostic factor for PFS and overall survival in not only transplant-eligible but also transplant-ineligible patients, as well as in the relapse setting,” he said.³ If sustained for a longer period of time, MRD negativity may indicate a greater level of disease control.³

“[Results from] both MAIA and ALCYONE individually, as well as in the pooled analysis, [showed that] durable minimal residual disease [MRD] negativity lasting for more than 6 months improved PFS compared with MRD-negative patients who did not maintain MRD negativity for more than 6 months.”

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The large data sets from MAIA and ALCYONE were used in the pooled analysis to evaluate the role of predictive and prognostic values of MRD negativity and durability.³ In the studies, MRD had been assessed in patients who achieved a complete response (CR) or stringent CR. Timed from the date of receiving the first dose, the assessments were given at months 12, 18, 24, and 30 in both studies and also months 36, 48, and 60 in the MAIA study. For each MRD assessment, researchers used the clonoSEQ assay version 2.0 at the 10^{-5} threshold for next-generation sequencing.³

The patients had NDMM and were ineligible to receive high-dose chemotherapy with a stem cell transplant because of their age (65 years and older) or because of a comorbid condition that disqualified them.³ Patient baseline characteristics included age, disease stage as classified by the International Staging System, and cytogenetic

profile.³ “The baseline characteristics for the MRD-negative patients in MAIA were comparable with the intention-to-treat population,” noted San-Miguel. “The same applied for the ALCYONE study.”³

In MAIA, 737 patients were randomized to receive Rd (n = 369) or D-Rd (n = 368) in 28-day cycles. Median duration of follow-up was 36.4 months (range, 0.0-49.9). In ALCYONE, 706 were randomized to receive VMP (n = 356; in 6-week cycles up to 9 times) or D-VMP (n = 350; up to 9 cycles combined with VMP, followed by DARA alone). Median duration of follow-up was 40.1 months (range, 0.0-52.1). Treatments were administered until disease progression or intolerable toxicity.³

Results from “both MAIA and ALCYONE individually, as well as in the pooled analysis, [showed that] durable MRD negativity lasting for more than 6 months improved PFS compared with MRD-negative patients who did not maintain MRD negativity for more than 6 months,” said San-Miguel. “The same picture [was] observed for patients with MRD negativity lasting for more than 12 months.”³ This was irrespective of which treatment arm the patients participated in.³ In addition, MRD negativity was associated with higher estimated 36-month rates of PFS on next subsequent line of therapy than that of MRD positivity, regardless of treatment.³

San-Miguel stated that although “patients who achieved CR or greater and MRD negativity had improved PFS regardless of treatment regimen, patients who achieved CR plus MRD negativity and received DARA had improved PFS vs those who only received the standard of care” (HR, 0.51; 95% CI, 0.28-0.92; $P = .0253$).³ At 6 months or more, sustained MRD negativity was achieved by 14.9% of patients receiving D-Rd vs 4.3% receiving Rd ($P < .0001$) and 15.7% receiving D-VMP versus 4.5% receiving VMP ($P < .0001$). At 12 months or more, sustained MRD negativity was achieved by 10.9% of patients receiving D-Rd versus 2.4% receiving Rd ($P < .0001$) and 14.0% receiving D-VMP versus 2.8% receiving VMP ($P < .0001$). Regarding the VMP regimens, the improvements associated with DARA were potentially influenced by therapy duration; the D-VMP regimen was administered until disease progression, whereas the VMP-only regimen was given for 9 cycles.³

MRD-negative status was associated with longer PFS, particularly when MRD was sustained for 6 months or more or 12 months or more. This was true for all treatment regimens, but DARA-based regimens achieved higher rates of MRD negativity and sustained MRD negativity. “These analyses clearly support the view that MRD negativity, if sustained over time, reflects a robust measure of disease control,” said San Miguel. “[MRD negativity] should also be considered in the context of hematologic response.”³ ♦

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Study Authors Report Real-World Outcomes and Practice Patterns of CNS Prophylaxis in Aggressive Non-Hodgkin Lymphoma

By Brian Dunleavy, MA

CENTRAL NERVOUS SYSTEM (CNS) prophylaxis does not reduce the risk for relapse in patients with aggressive non-Hodgkin lymphoma (NHL), regardless of the route of administration. The finding was presented during the 62nd American Society of Hematology Annual Meeting and Exposition, held online due to the coronavirus disease 2019 pandemic.¹

Among 1030 patients treated for NHL, who received either R-CHOP (rituximab plus cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate [oncovin], and prednisone; 45.9%) or REPOCH (rituximab plus etoposide phosphate, prednisone, vincristine sulfate [oncovin], cyclophosphamide, and doxorubicin hydrochloride; 46.5%), 5.3% experienced a CNS relapse. Relapse rates were similar for both intravenous (IV) prophylaxis (7%) and intrathecal (IT) prophylaxis (5%), according to Orellana-Noia and colleagues.¹

“We observed no significant difference in CNS relapse incidence between routes of administration,” said Victor M. Orellana-Noia, MD, an instructor in the Department of Hematology and Medical Oncology at Winship Cancer Institute of Emory University in Atlanta, Georgia. “These data highlight some of the shortcomings in our current prognostication modeling and how they manifest in terms of CNS relapse after single-route CNS prophylaxis. We cannot say yet which patients should or should not receive prophylaxis—this study was not designed to answer that question—though it is becoming

increasingly clear that for high-risk patients, we need to figure out whether a methotrexate-based prophylactic approach makes sense.”

In the rituximab era, CNS relapse occurs in approximately 5% of patients with aggressive NHL, but rates rise to just above 10% among those in high-risk groups based on histologic subtype and subtype-specific clinicopathologic features (eg, site of involvement). Generally, CNS relapse occurs during the first 4 to 6 months after initial diagnosis.²⁻⁴

To date, the administration, route, and dosing schedule for CNS prophylaxis in patients with aggressive NHL has not been standardized, according to the investigators. For this multicenter retrospective analysis, they reviewed data on 1030 patients with the disease (excluding those with Burkitt lymphoma)—but without known CNS involvement—treated with single-route CNS prophylaxis as part of frontline anthracycline-based therapy at 19 US academic hospitals between 2013 and 2019. Patients who had received chemotherapy for prior B-cell chronic lymphocytic leukemia or indolent NHL were excluded from the study.¹

The investigators evaluated method, frequency, and outcomes of CNS prophylaxis administration, assessing significance by various statistical methods via 2-tailed $P < .05$. Clinical features of study participants included a median age of 61 years (range, 16-86 years), female (40.9% of participants), an Eastern Cooperative Oncology

Group performance status score of 0 to 1 (82.8% of study participants), and elevated serum lactate dehydrogenase (LDH; 65.3% of participants). In addition, 42.3% had more than 1 extranodal (EN) site, and 79.2% had stage 3/4 disease. In all, 85.7% of participants had EN involvement, with the most common sites being bone (35.4%), liver (13.7%), gastrointestinal (12.7%), lung (11.8%), and marrow (11.5%).¹

NHL histologies included diffuse large B-cell lymphoma (DLBCL; 75.2% of participants), high-grade B-cell lymphoma (16.3%), transformed follicular lymphoma (5.6%), and other (3%). Among participants with DLBCL, 46.4% had germinal center subtype. In all, 26.2% of evaluable participants had double-hit lymphoma (DHL). Among study participants for whom HIV status was known, 7.2% were HIV positive.¹

Prophylaxis was delivered via IV administration in 20% of the patients and via IT administration in 77%, for a median 2.9 versus 4.1 doses, respectively. Patients in the IT group were slightly older than those in the IV group (median age, 59.6 years vs 57 years), and a higher percentage had DHL or triple-hit lymphoma (23.1% vs 8.9%, respectively). Conversely, more patients in the IV group had more than 1 EN site (55% vs 39.1%) and normal renal function (81.2% vs 71.4%).¹

In general, prophylaxis was well tolerated, with 10.7% of study patients reporting toxicities. The most common toxicities in the IV group were renal (13.3%), delayed methotrexate clearance (6.9%), cytopenias delaying the next chemotherapy cycle (4.5%), and severe mucositis (4%). In the IT group, the most common reported toxicities were severe, treatment-limiting headache (2.1%), cytopenias delaying the next chemotherapy cycle (1.5%), and peripheral neuropathy (1.3%).¹

In all subgroup analyses, investigators observed a lack of difference in relapse rates between prophylaxis routes, including age, stage, histology, number of EN sites, individual EN site involvement, elevated LDH level, CNS International Prognostic Index (CNS-IPI) score, DHL status, HIV status, frontline regimen, and number of doses. In addition, there was no significant difference in anatomic site(s) of CNS relapse by prophylaxis route.¹

CNS relapse was diagnosed by the end of frontline treatment in 24% of study patients and was delayed in 76% (average, 2.3 years). Overall, rates of CNS relapse were significantly higher with CNS-IPI high- versus moderate-risk score (8.3% vs 4.1%; $P = .03$), elevated LDH level (6.9% vs 2.6%; $P = .007$), and multiple EN site involvement (7.5% for ≥ 2 vs 4% for 0-1; $P = .01$). Also, each additional EN site further increased risk trend ($P = .03$), with increased CNS relapse observed in patients with testis involvement

(13.7% vs 5%, $P = .004$) and liver involvement (11.1% vs 4.6%; $P = .002$) versus those without involvement at these sites. The investigators noted no significant difference at other EN sites.¹

With a median follow-up of 2.3 years, median progression-free survival and overall survival for study patients have not been reached; however, at 2 years, progression-free survival and overall survival were 70% and 85%, respectively. Further, 196 deaths were reported, including 122 disease related and 34 treatment related (1.9% IV vs 3.6% IT; $P = .24$). Death due to progression was more common following IT prophylaxis (13.3%; $P = .04$) than IV prophylaxis (7.9%; $P = .04$), and this was driven primarily by DH status (hazard ratio, 1.54; $P = .11$). Perhaps not surprisingly, in those with CNS relapse, subsequent relapse and/or death was common (74.5%) regardless of initial prophylaxis route or salvage therapy. Median survival after CNS relapse diagnosis was 7.1 months and was significantly lower than that in patients without relapse ($P = .03$).¹

“These data highlight some of the shortcomings in our current prognostication modeling and how they manifest in terms of CNS relapse after single-route CNS prophylaxis.”

— Victor M. Orellana-Noia, MD
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“Which patients and what routes of CNS prophylaxis we offer patients continue to vary in ways that can be challenging to quantify,” Orellana-Noia said. “Deciding who is high enough risk to justify prophylaxis is part of the challenge, and I think we can do better at standardizing that. Right now, when we talk about CNS prophylaxis, it comes down to how we’re going to give methotrexate, but I think a number of studies recently, including ours, have shown we need to be thinking beyond this. We have at least a couple other agents which have well-known CNS penetration and clear antilymphoma effect. How we leverage that to preventing what is clearly a devastating outcome will be our next big step.” ♦

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Investigators Assess Disease Severity and Mortality by ABO Blood Group in Hospitalized Patients With COVID-19

By Samantha Stone, PhD

CORONAVIRUS DISEASE 2019 (COVID-19) has been associated with acute hypoxemic respiratory failure, leading to the use of invasive mechanical ventilation, intensive care unit (ICU) admissions, and death in some patients.

Early observational studies have suggested a correlation between COVID-19 vulnerability and type A blood group, with increased risk of respiratory failure and poor health outcomes.

However, data presented at the 62nd American Society of Hematology Annual Meeting and Exposition from a retrospective analysis of hospitalized patients with COVID-19 found no significant correlations among ABO blood groups, mechanical ventilation use, or disease severity and mortality in hospitalized patients with COVID-19.¹

Aula Ramo, MD, of Henry Ford Hospital in Detroit, Michigan, the lead study author, explained that the rationale for the presented retrospective analysis was that “as the pandemic started, multiple studies were coming out with different findings in regard to associations between ABO blood groups and COVID-19 in terms of disease susceptibility as well as disease severity.”

Ramo went on to state that “there were variables that were hard to control and vary from study to study,” which may affect results and could account for some of the inconsistency noted in this arena. She highlighted “variable definitions of what defines disease severity in terms of ICU admission, availability of ICU beds, and the nonstandardized treatment of COVID-19” as the major contributing variables.

In order to examine ABO blood group designation in relation to COVID-19 disease severity and mortality, data from 1488 patients confirmed with polymerase chain reaction to have COVID-19 between March 10 and April 30, 2020, hospitalized in the Henry Ford Health System main campus and metropolitan locations, were examined. Data on age, gender, race, ABO blood group, underlying comorbidities, disease severity (defined as intensive care unit admission), need for intubation, and mortality were collected.

The median age of the patients within the analysis was 68 years (range, 19-99), and more than half of the study population were women (54%; n = 801). African American patients accounted for 58% of the population (n = 856) under investigation. Patients with blood group O accounted for the greatest percentage of patients at 44.2% (n = 658), with blood groups A, B, and AB accounting for 32.6% (n = 485), 18.5% (n = 276), and 4.6% (n = 69), respectively. Within the study period, 31.5% of patients were admitted to the ICU (n = 469), with 370 requiring intubations. On the date of last follow-up (July 15, 2020), 27.6% of the studied patient population (n = 411) were deceased.

Studied comorbidities included coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), hypertension, hyperlipidemia, obesity, diabetes, renal insufficiency, autoimmune diseases, malignancy, and a history of transplant.

In a univariate analysis, noted predictors of mortality included male sex (odds ratio [OR], 1.75; 95% CI, 1.39-2.20; $P < .001$), 65 years or older (OR, 5.0; 95% CI, 3.78-6.63; $P < .001$), Caucasian descent (OR, 1.79; 95% CI, 1.42-2.25;

$P < .001$), and certain underlying conditions. Of the comorbidities examined, only CAD (OR, 1.83; 95% CI, 1.41-2.38), COPD (OR, 1.82; 95% CI, 1.36-2.44), obesity (OR, 0.57; 95% CI, 0.44-0.74), and malignancy (OR, 1.75; 95% CI, 1.32-2.33) were seen to be significantly correlated with rates of mortality ($P < .001$). Cramer V was used to assess the correlation between ABO blood group and rate of mortality, in the univariate analysis, with no significant correlation reached ($P = .03$). A nonsignificant correlation was also demonstrated for a patient's risk for intubation.

These associations were upheld in a separate multivariate analysis where male sex (OR, 1.57; 95% CI, 1.23-2.01; $P < .001$), age of 65 years or older (OR, 4.27; 95% CI, 3.19-5.71; $P < .001$), Caucasian descent (OR, 1.46; 95% CI, 1.14-1.86; $P = .003$), or having COPD (OR, 1.49; 95% CI, 1.09-2.04; $P = .013$) were significantly associated with mortality. Of note in this analysis, African American patients with COVID-19 infection demonstrated a more than 40% reduction in mortality (OR, 0.56; 95% CI, 0.44-0.70; $P < .001$) compared with Caucasian patients.

Additionally, the study authors noted that neither ABO blood group nor Rhesus factor (D antigen) was associated

with ICU admission, intubation risk, or death in the patient population (no statistical analysis was presented for these data). Overall, the study authors concluded that in this analysis, the predictors of mortality due to COVID-19 leading to an increased risk of death were being male, 65 years or older, and of Caucasian descent.

Walter Dzik, MD, an associate pathologist at Massachusetts General Hospital, emphasized that “this study correctly compares COVID versus COVID patients” while similar published studies “compared COVID versus normal blood donors.”

The study authors hope to expand on the presented results with a larger patient population and to incorporate measurements of thromboembolism, bleeding, and hypercoagulability into the investigation. ♦

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Findings Clarify Tyrosine Kinase Inhibitor Use in Older Patients With Chronic Myeloid Leukemia

By Laurie Saloman, MS

BCR-ABL1 TYROSINE KINASE INHIBITORS (TKIs) are a standard first-line therapy for patients with chronic myeloid leukemia (CML). However, some practitioners are reluctant to prescribe TKIs to elderly patients, possibly due to fears of potential adverse effects and complications such as cardiovascular problems.^{1,2} As approximately half of all patients who receive a CML diagnosis are at least 65 years old at the time; this represents a large pool of patients who might benefit from TKIs. Unfortunately, data on individuals who don't receive TKI therapy are lacking.²

Knowing that TKI therapy gives patients with CML who are in the chronic phase of their disease roughly the same survival odds as those in the general population, a team of investigators at Yale School of Medicine in New Haven, Connecticut, conducted a study that sheds light on the characteristics of older patients with CML who are likely to receive a TKI. Rory Shallis, MD, an assistant professor of medicine, hematology, at Yale

School of Medicine and an author of the study, presented the study's abstract at the 62nd American Society of Hematology Annual Meeting and Exposition, held virtually December 5 to 8, 2020. “We know that some patients never receive a TKI [because of] factors [such as] frailty [or] comorbidity, and consequently, the likelihood of treatment-related morbidity possibly [predicts] lack of TKI receipt,” said Shallis.²

The study had several hypotheses, including that lack of TKI treatment initiation in older patients with CML would be associated with acute issues at diagnosis that would portend a very brief life expectancy; that increased age and elevated burden of comorbidity would be associated with a lesser chance of receiving a TKI, both due to older age itself and its typically higher comorbidity burden; and that use of a TKI would increase during the study due to greater availability, choice in TKIs, and more experience with TKIs as the years progressed.²

Study data came from the SEER database, which is linked to Medicare. Included were 1075 subjects who had received a diagnosis of CML between 2007 and 2015, ranging in age from 66 to 99 years at diagnosis, with a median age of 76. Thirty-five percent were aged 80 or older, slightly more than half were women, and the overwhelming majority (87.4%) were white. The subjects all had continuous Medicare coverage; about a third received low-income subsidies. None of the subjects had received a TKI within 3 months of diagnosis. They were followed for at least 90 days; until the trial's end on December 31, 2016; until they had a change of insurance; or until they died—whichever occurred first. The median follow-up time was 2.67 years.²

Of 1075 patients in the study, 75% (n = 810) were given TKIs after diagnosis. This proportion increased from 62.9% receiving a TKI in 2007 at the beginning of the study to 77.4% at the end of the study in 2015. Patients who received a TKI had significantly longer survival time (6.72 [5.91-7.56] vs 1.93 [1.44-2.31], respectively; 95% CI, $P < .01$). The median survival in patients receiving a TKI was 6.72 years; without a TKI, 1.93 years. Overall, among patients receiving a TKI, 26.8% of subjects died from CML and 17.7% due to heart disease.²

The team then performed a subanalysis of only patients who were followed for at least 6 months, in order to exclude patients who might not have received a TKI due to acute issues or other factors that would have precluded the use of such therapy. The results were close to the results of the study population as a whole, with a median survival of TKI recipients of about 7 years and a median survival of those who didn't receive TKI of about 2.5 years.²

The study used multivariable competing risk regression models when looking at variables associated with the use of a TKI. These included race, sex, age at diagnosis, year of diagnosis, marital status, location, income subsidies, local poverty levels, whether the patient had received an influenza vaccine before diagnosis, and whether the patients lived in a rural or an urban area. The investigators also took into account whether the patients had other malignancies and diseases such as cardiovascular or pulmonary conditions. When examining the common comorbidities they deemed likely to influence whether a provider would prescribe a TKI, they found that 27.1% of patients had received a diagnosis of some form of cardiovascular disease and 82.1% had cardiovascular disease risk factors such as smoking, hypertension, hyperlipidemia, and diabetes.²

“In evaluating the variables associated with TKI receipt among patients in our cohort, we found that increasing age and being unmarried were associated with a lesser probability of receiving a TKI, whereas being diagnosed later during our study time frame was associated with a greater

likelihood of receiving a TKI,” Shallis said. “Similarly, receiving an influenza vaccination prior to diagnosis, a surrogate for general access to health care, as well as having a low-income subsidy, was associated with a greater likelihood of TKI receipt.”²

Factors not predictive of TKI receipt included race, sex, other malignancies, cardiovascular or pulmonary disease, cardiovascular disease risk factors, local poverty levels, location, and living in an urban or rural area.²

“In evaluating the variables associated with tyrosine kinase inhibitor [TKI] receipt among patients in our cohort, we found that increasing age and being unmarried were associated with a lesser probability of receiving a TKI, whereas being diagnosed later during our study time frame was associated with a greater likelihood of receiving a TKI.”

— Rory Shallis, MD
Yale School of Medicine
New Haven, Connecticut

The study's strengths include its size and ability to capture a real-world experience incorporating a robust range of relevant covariates. “Despite the strengths, there are some limitations, such as the absence of other disease-related factors [such as] phase of disease or other biological metrics,” Shallis said. “Importantly, we were unable to capture physician intent or the concrete reason as to why a patient did not receive a TKI. We were only left to infer based on our analyses.”² ♦

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Emerging GRIFFIN Study Data Support Efficacy, Safety of D-RVd in Transplant-Eligible, Newly Diagnosed Multiple Myeloma

By Brian Dunleavy, MA

THE HUMAN IMMUNOGLOBULIN G KAPPA monoclonal antibody daratumumab targets CD38 and is approved in combination with bortezomib, thalidomide, and dexamethasone for patients with transplant-eligible, newly diagnosed multiple myeloma (NDMM). Despite this approval, the standard of care in the United States for this population is lenalidomide, bortezomib, and dexamethasone (RVd).¹

Durable responses were observed in patients with transplant-eligible NDMM who had undergone autologous stem cell transplant (ASCT) and were treated with daratumumab plus RVd (D-RVd) induction therapy, ASCT, and consolidation, according to findings from the phase 2 GRIFFIN trial (NCT02874742) presented by Peter M. Voorhees, MD of Levine Cancer Institute, Atrium Health, Charlotte, North Carolina, at the 62nd American Society of Hematology Annual Meeting and Exposition.¹

The GRIFFIN study included a safety run-in phase followed by a randomized phase.¹ Sixteen patients were included in the safety run-in phase, with no dose-limiting toxicities and no new safety concerns observed with D-RVd.^{1,2} In the randomized phase of the trial (N = 207), the regimen demonstrated improved rate of stringent complete response (sCR) by the end of consolidation (42.4% in D-RVd group vs 32% in RVd group; 1-sided $P = .068$).^{1,3} The median follow-up was limited at 13.5 months. Trial investigators performed an updated efficacy and safety analysis of the safety run-in group to analyze longer follow-up data for D-RVd and evaluate the potential role of daratumumab plus lenalidomide (D-R) maintenance therapy in patients with transplant-eligible NDMM.¹

Investigators assessed outcomes in the 16 patients who were eligible for high-dose therapy and ASCT. All patients in the cohort received 4 induction cycles of D-RVd, high-dose therapy, ASCT, 2 consolidation cycles of D-RVd, and 24 months of D-R maintenance therapy. During the induction and consolidation phases of treatment, patients were given 25 mg of lenalidomide orally on days 1 through 14; 1.3 mg/m² of subcutaneous bortezomib on days 1, 4, 8, and 11; and 40 mg of dexamethasone once weekly every 21 days. In addition, 16 mg/kg of intravenous (IV) daratumumab was administered on days 1, 8, and 15 of cycles 1 through 4 and day 1 of cycles 5 and 6. During the

maintenance therapy phase (cycles 7-32), patients received 10 mg of lenalidomide (15 mg in cycles 10 and later if tolerated) on days 1 through 21 every 28 days and 16 mg/kg of daratumumab IV 8 times weekly (or 4 times weekly per patient decision).

The primary end point was the analysis of dose-limiting toxicities, and additional end points included safety, sCR rate by the end of the consolidation and maintenance phase per International Myeloma Working Group criteria, progression-free survival (PFS), and minimal residual disease (MRD) negativity (10^{-5} and 10^{-6} threshold) based on next-generation sequencing.¹

“These long-term, positive results, together with the results of the GRIFFIN randomized phase, support D-RVd as a potential new standard of care for patients with transplant-eligible, newly diagnosed multiple myeloma.”

— Peter M. Voorhees, MD
Levine Cancer Institute
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The median age of enrolled patients was 62.5 years, 4 had International Staging System stage II or III disease, and 4 had high cytogenetic risk established by fluorescence in situ hybridization. In total, 13 patients completed the study treatment, and 3 patients discontinued therapy due to disease progression (n = 2) or an adverse event (AE; n = 1). Responses advanced with continued D-RVd therapy. All patients responded by the completion of D-RVd consolidation, with sCR in 9 patients. Fifteen patients achieved a best response of sCR at the completion of D-R maintenance therapy. At consolidation completion, MRD negativity at 10^{-5} was in 8 patients, with no patient experiencing MRD negativity at 10^{-6} . Thirteen patients were MRD negative at 10^{-5} and 5 were MRD negative at 10^{-6} at completion of the

maintenance phase. Three patients experienced disease progression, with approximate 24-month and 36-month PFS rates of 94% and 78% at a median follow-up of 39 months, respectively. Disease progression caused 1 death during the study, in the patient who failed to achieve sCR.¹

No new safety concerns were noted with longer follow-up, although grade 3 and 4 treatment-emergent AEs (TEAEs) were observed in 14 patients. The most frequent TEAEs were neutropenia (n = 7), pneumonia (n = 5), lymphopenia (n = 4), and thrombocytopenia (n = 4). No grade 5 TEAEs were observed, the investigators reported. However, mostly during the first cycle, grade 1 and 2 infusion-related AEs took place in 4 patients.¹

“These long-term, positive results, together with the results of the GRIFFIN randomized phase, support D-RVd as a potential new standard of care for patients with transplant-eligible, newly diagnosed multiple myeloma,” Voorhees concluded.¹ ♦

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