Present-day Challenges in the Treatment of MM p.11

Multiple Myeloma TODAY

A quarterly publication for **healthcare professionals** focused on the latest news in Multiple Myeloma

Fall 2021
multiplemyelomatoday.com

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Exclusive content from The Leukemia & Lymphoma Society

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For appropriate patients faced with relapsed/refractory multiple myeloma

FORGE AHEAD WITH A BOLD APPROACH

Target BCMA for RRMM

BLENREP is the first and only BCMA-targeted ADC monotherapy. So you can offer your RRMM patients a different option.

INDICATION

BLENREP is indicated for the treatment of adults with relapsed or refractory multiple myeloma who have received at least 4 prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.

This indication is approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

IMPORTANT SAFETY INFORMATION

WARNING: OCULAR TOXICITY

BLENREP caused changes in the corneal epithelium resulting in changes in vision, including severe vision loss and corneal ulcer, and symptoms such as blurred vision and dry eyes.

Conduct ophthalmic exams at baseline, prior to each dose, and promptly for worsening symptoms. Withhold BLENREP until improvement and resume, or permanently discontinue, based on severity.

Because of the risk of ocular toxicity, BLENREP is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the BLENREP REMS.

ADC=antibody-drug conjugate; BCMA=B-cell maturation antigen; RRMM=relapsed or refractory multiple myeloma.

Learn more at **BLENREPHCP.com**

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Ocular Toxicity: Ocular adverse reactions occurred in 77% of the 218 patients in the pooled safety population. Ocular adverse reactions included keratopathy (76%), changes in visual acuity (55%), blurred vision (27%), and dry eye (19%). Among patients with keratopathy (n = 165), 49% had ocular symptoms, 65% had clinically relevant visual acuity changes (decline of 2 or more lines on Snellen Visual Acuity in any eye), and 34% had both ocular symptoms and visual acuity changes.

Keratopathy: Keratopathy was reported as Grade 1 in 7% of patients, Grade 2 in 22%, Grade 3 in 45%, and Grade 4 in 0.5% per the KVA scale. Cases of corneal ulcer (ulcerative and infective keratitis) have been reported. Most keratopathy events developed within the first 2 treatment cycles (cumulative incidence of 65% by Cycle 2). Of the patients with Grade 2 to 4 keratopathy (n = 149), 39% recovered to Grade 1 or lower after median follow-up of 6.2 months. Of the 61% who had ongoing keratopathy, 28% were still on treatment, 9% were in follow-up, and in 24% the follow-up ended due to death, study withdrawal, or lost to follow-up. For patients in whom events resolved, the median time to resolution was 2 months (range: 11 days to 8.3 months).

Visual Acuity Changes: A clinically significant decrease in visual acuity of worse than 20/40 in the better-seeing eye was observed in 19% of the 218 patients and of 20/200 or worse in the better-seeing eye in 1.4%. Of the patients with decreased visual acuity of worse than 20/40, 88% resolved and the median time to resolution was 22 days (range: 7 days to 4.2 months). Of the patients with decreased visual acuity of 20/200 or worse, all resolved and the median duration was 22 days (range: 15 to 22 days).

Monitoring and Patient Instruction: Conduct ophthalmic examinations (visual acuity and slit lamp) at baseline, prior to each dose, and promptly for worsening symptoms. Perform baseline examinations within 3 weeks prior to the first dose. Perform each follow-up examination at least 1 week after the previous dose and within 2 weeks prior to the next dose. Withhold BLENREP until improvement and resume at same or reduced dose, or consider permanently discontinuing based on severity. Advise patients to use preservative-free lubricant eye drops at least 4 times a day starting with the first infusion and continuing until end of treatment. Avoid use of contact lenses unless directed by an ophthalmologist. Changes in visual acuity may be associated with difficulty for driving and reading. Advise patients to use caution when driving or operating machinery. BLENREP is only available through a restricted program under a REMS.

Thrombocytopenia: Thrombocytopenia occurred in 69% of 218 patients in the pooled safety population, including Grade 2 in 13%, Grade 3 in 10%, and Grade 4 in 17%. The median time to onset of the first thrombocytopenic event was 26.5 days. Thrombocytopenia resulted in dose reduction, dose interruption, or discontinuation in 9%, 2.8%, and 0.5% of patients, respectively. Grade 3 to 4 bleeding events occurred in 6% of patients, including Grade 4 in 1 patient. Fatal adverse reactions included cerebral hemorrhage in 2 patients. Perform complete blood cell counts at baseline and during treatment as clinically indicated. Consider withholding and/or reducing the dose based on severity.

Infusion-Related Reactions: Infusion-related reactions occurred in 18% of 218 patients in the pooled safety population, including Grade 3 in 1.8%. Monitor patients for infusion-related reactions. For Grade 2 or 3 reactions, interrupt the infusion and provide supportive treatment. Once symptoms resolve, resume at a lower infusion rate. Administer premedication for all subsequent infusions. Discontinue BLENREP for life-threatening infusion-related reactions and provide appropriate emergency care.

Embryo-Fetal Toxicity: Based on its mechanism of action, BLENREP can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus.

Advise females of reproductive potential to use effective contraception during treatment with BLENREP and for 4 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with BLENREP and for 6 months after the last dose. Pregnancy testing is recommended for females of reproductive potential prior to initiating BLENREP.

ADVERSE REACTIONS

The pooled safety population described in *Warnings and Precautions* reflects exposure to BLENREP at a dosage of 2.5 mg/kg or 3.4 mg/kg (1.4 times the recommended dose) administered intravenously once every 3 weeks in 218 patients in DREAMM-2. Of these patients, 194 received a liquid formulation (not the approved dosage form) rather than the lyophilized powder.

Patients received BLENREP at the recommended dosage of 2.5 mg/kg administered intravenously once every 3 weeks (n = 95). Permanent discontinuation due to an adverse reaction occurred in 8% of patients who received BLENREP; keratopathy (2.1%) was the most frequent adverse reaction resulting in permanent discontinuation. Dosage interruptions due to an adverse reaction occurred in 54% of patients who received BLENREP. Adverse reactions which required a dosage interruption in >3% of patients included keratopathy (47%), blurred vision (5%), dry eye (3.2%), and pneumonia (3.2%). Dose reductions due to an adverse reaction occurred in 29% of patients. Adverse reactions which required a dose reduction in >3% of patients included keratopathy (23%) and thrombocytopenia (5%).

The most common adverse reactions (≥20%) were keratopathy (71%), decreased visual acuity (53%), nausea (24%), blurred vision (22%), pyrexia (22%), infusion-related reactions (21%), and fatigue (20%). The most common Grade 3 or 4 (≥5%) laboratory abnormalities were lymphocytes decreased (22%), platelets decreased (21%), hemoglobin decreased (18%), neutrophils decreased (9%), creatinine increased (5%), and gamma-glutamyl transferase increased (5%).

Serious adverse reactions occurred in 40% of patients who received BLENREP. Serious adverse reactions in >3% of patients included pneumonia (7%), pyrexia (6%), renal impairment (4.2%), sepsis (4.2%), hypercalcemia (4.2%), and infusion-related reactions (3.2%). Fatal adverse reactions occurred in 3.2% of patients, including sepsis (1%), cardiac arrest (1%), and lung infection (1%).

USE IN SPECIFIC POPULATIONS

Lactation: Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with BLENREP and for 3 months after the last dose.

Females and Males of Reproductive Potential: Based on findings in animal studies, BLENREP may impair fertility in females and males.

Geriatric Use: Of the 218 patients who received BLENREP in DREAMM-2, 43% were aged 65 to less than 75 years and 17% were aged 75 years and older. Keratopathy occurred in 80% of patients aged less than 65 years and 73% of patients aged 65 years and older. Among the 95 patients who received BLENREP at the 2.5-mg/kg dose, keratopathy occurred in 67% of patients aged less than 65 years and 73% of patients aged 65 years and older.

Renal or Hepatic Impairment: The recommended dosage has not been established in patients with severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2) or end-stage renal disease (ESRD) with eGFR <15 mL/min/1.73 m^2 not on dialysis or requiring dialysis. The recommended dosage has not been established in patients with moderate or severe hepatic impairment (total bilirubin >1.5 × ULN and any AST).

Please see Brief Summary of full Prescribing Information, including BOXED WARNING, on the following pages.

BLENREP
belantamab
mafodotin-blmf
for injection 100 mg

Made for this Moment

BRIEF SUMMARY

BLENREP

(belantamab mafodotin-blmf)
for injection, for intravenous use

The following is a brief summary only; see full Prescribing Information for complete product information.

WARNING: OCULAR TOXICITY

BLENREP caused changes in the corneal epithelium resulting in changes in vision, including severe vision loss and corneal ulcer, and symptoms, such as blurred vision and dry eyes *[see Warnings and Precautions (5.1)]*.

Conduct ophthalmic exams at baseline, prior to each dose, and promptly for worsening symptoms. Withhold BLENREP until improvement and resume, or permanently discontinue, based on severity *[see Dosage and Administration (2.3) of full Prescribing Information, Warnings and Precautions (5.1)]*.

Because of the risk of ocular toxicity, BLENREP is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the BLENREP REMS *[see Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

BLENREP is indicated for the treatment of adults with relapsed or refractory multiple myeloma who have received at least 4 prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.

This indication is approved under accelerated approval based on response rate *[see Clinical Studies (14) of full Prescribing Information]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Ocular Toxicity

Ocular adverse reactions occurred in 77% of the 218 patients in the pooled safety population. Ocular adverse reactions included keratopathy (76%), changes in visual acuity (55%), blurred vision (27%), and dry eye (19%) *[see Adverse Reactions (6.1)]*. Among patients with keratopathy (n = 165), 49% had ocular symptoms, 65% had clinically relevant visual acuity changes (decline of 2 or more lines on Snellen Visual Acuity in any eye), and 34% had both ocular symptoms and visual acuity changes.

Keratopathy

Keratopathy was reported as Grade 1 in 7% of patients, Grade 2 in 22%, Grade 3 in 45%, and Grade 4 in 0.5% per the KVA scale. Cases of corneal ulcer (ulcerative and infective keratitis) have been reported. Most keratopathy events developed within the first 2 treatment cycles (cumulative incidence of 65% by Cycle 2). Of the patients with Grade 2 to 4 keratopathy (n = 149), 39% of patients recovered to Grade 1 or lower after median follow-up of 6.2 months. Of the 61% who had ongoing keratopathy, 28% were still on treatment, 9% were in follow-up, and in 24% the follow-up ended due to death, study withdrawal, or lost to follow up. For patients in whom events resolved, the median time to resolution was 2 months (range: 11 days to 8.3 months).

Visual Acuity Changes

A clinically significant decrease in visual acuity of worse than 20/40 in the better-seeing eye was observed in 19% of the 218 patients and of 20/200 or worse in the better-seeing eye in 1.4%. Of the patients with decreased visual acuity of worse than 20/40, 88% resolved and the median time to resolution was 22 days (range: 7 days to 4.2 months). Of the patients with decreased visual acuity of 20/200 or worse, all resolved and the median duration was 22 days (range: 15 to 22 days).

Monitoring and Patient Instruction

Conduct ophthalmic examinations (visual acuity and slit lamp) at baseline, prior to each dose, and promptly for worsening symptoms. Perform baseline examinations within 3 weeks prior to the first dose. Perform each follow-up examination at least 1 week after the previous dose and within 2 weeks prior to the next dose. Withhold BLENREP until improvement and resume at same or reduced dose, or consider permanently discontinuing based on severity *[see Dosage and Administration (2.3) of full Prescribing Information]*.

Advise patients to use preservative-free lubricant eye drops at least 4 times a day starting with the first infusion and continuing until end of treatment. Avoid use of contact lenses unless directed by an ophthalmologist *[see Dosage and Administration (2.1) of full Prescribing Information]*.

Changes in visual acuity may be associated with difficulty for driving and reading. Advise patients to use caution when driving or operating machinery.

BLENREP is only available through a restricted program under a REMS *[see Warnings and Precautions (5.2)]*.

5.2 BLENREP REMS

BLENREP is available only through a restricted program under a REMS called the BLENREP REMS because of the risks of ocular toxicity *[see Warnings and Precautions (5.1)]*.

Notable requirements of the BLENREP REMS include the following:

- Prescribers must be certified with the program by enrolling and completing training in the BLENREP REMS.
- Prescribers must counsel patients receiving BLENREP about the risk of ocular toxicity and the need for ophthalmic examinations prior to each dose.
- Patients must be enrolled in the BLENREP REMS and comply with monitoring.
- Healthcare facilities must be certified with the program and verify that patients are authorized to receive BLENREP.
- Wholesalers and distributers must only distribute BLENREP to certified healthcare facilities.

Further information is available, at www.BLENREPREMS.com and 1-855-209-9188.

5.3 Thrombocytopenia

Thrombocytopenia occurred in 69% of 218 patients in the pooled safety population, including Grade 2 in 13%, Grade 3 in 10%, and Grade 4 in 17% *[see Adverse Reactions (6.1)]*. The median time to onset of the first thrombocytopenic event was 26.5 days. Thrombocytopenia resulted in dose reduction, dose interruption, or discontinuation in 9%, 2.8%, and 0.5% of patients, respectively.

Grade 3 to 4 bleeding events occurred in 6% of patients, including Grade 4 in 1 patient. Fatal adverse reactions included cerebral hemorrhage in 2 patients.

Perform complete blood cell counts at baseline and during treatment as clinically indicated. Consider withholding and/or reducing the dose based on severity *[see Dosage and Administration (2.3) of full Prescribing Information]*.

5.4 Infusion-Related Reactions

Infusion-related reactions occurred in 18% of 218 patients in the pooled safety population, including Grade 3 in 1.8% *[see Adverse Reactions (6.1)]*.

Monitor patients for infusion-related reactions. For Grade 2 or 3 reactions, interrupt the infusion and provide supportive treatment. Once symptoms resolve, resume at a lower infusion rate *[see Dosage and Administration (2.3) of full Prescribing Information]*. Administer premedication for all subsequent infusions. Discontinue BLENREP for life-threatening infusion-related reactions and provide appropriate emergency care.

5.5 Embryo-Fetal Toxicity

Based on its mechanism of action, BLENREP can cause fetal harm when administered to a pregnant woman because it contains a genotoxic compound (the microtubule inhibitor, monomethyl auristatin F [MMAF]) and it targets actively dividing cells.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with BLENREP and for 4 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with BLENREP and for 6 months after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Ocular toxicity *[see Warnings and Precautions (5.1)]*.
- Thrombocytopenia *[see Warnings and Precautions (5.3)]*.
- Infusion-related reactions *[see Warnings and Precautions (5.4)]*.

6.1 Clinical Trials Experience

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

The pooled safety population described in *Warnings and Precautions* reflects exposure to BLENREP at a dosage of 2.5 mg/kg or 3.4 mg/kg (1.4 times the recommended dose) administered intravenously once every 3 weeks in 218 patients in DREAMM-2. Of these patients, 194 received a liquid formulation (not the approved dosage form) rather than the lyophilized powder. Among the 218 patients, 24% were exposed for 6 months or longer.

Relapsed or Refractory Multiple Myeloma

The safety of BLENREP as a single agent was evaluated in DREAMM-2 *[see Clinical Studies (14.1) of full Prescribing Information]*. Patients received BLENREP at the recommended dosage of 2.5 mg/kg administered intravenously once every 3 weeks (n = 95). Among these patients, 22% were exposed for 6 months or longer.

Serious adverse reactions occurred in 40% of patients who received BLENREP. Serious adverse reactions in >3% of patients included pneumonia (7%), pyrexia (6%), renal impairment (4.2%), sepsis (4.2%), hypercalcemia (4.2%), and infusion-related reactions (3.2%). Fatal adverse reactions occurred in 3.2% of patients, including sepsis (1%), cardiac arrest (1%), and lung infection (1%).

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Permanent discontinuation due to an adverse reaction occurred in 8% of patients who received BLENREP; keratopathy (2.1%) was the most frequent adverse reaction resulting in permanent discontinuation.

Dosage interruptions due to an adverse reaction occurred in 54% of patients who received BLENREP. Adverse reactions which required a dosage interruption in >3% of patients included keratopathy (47%), blurred vision (5%), dry eye (3.2%), and pneumonia (3.2%).

Dose reductions due to an adverse reaction occurred in 29% of patients. Adverse reactions which required a dose reduction in >3% of patients included keratopathy (23%) and thrombocytopenia (5%).

The most common adverse reactions (≥20%) were keratopathy, decreased visual acuity, nausea, blurred vision, pyrexia, infusion-related reactions, and fatigue. The most common Grade 3 or 4 (≥5%) laboratory abnormalities were lymphocytes decreased, platelets decreased, hemoglobin decreased, neutrophils decreased, creatinine increased, and gamma-glutamyl transferase increased.

Table 1 summarizes the adverse reactions in DREAMM-2 for patients who received the recommended dosage of 2.5 mg/kg once every 3 weeks.

Table 1. Adverse Reactions (≥10%) in Patients Who Received BLENREP in DREAMM-2

Adverse Reactions	BLENREP N = 95	
	All Grades (%)	Grade 3-4 (%)
Eye disorders		
Keratopathy[a]	71	44
Decreased visual acuity[b]	53	28
Blurred vision[c]	22	4
Dry eyes[d]	14	1
Gastrointestinal disorders		
Nausea	24	0
Constipation	13	0
Diarrhea	13	1
General disorders and administration site conditions		
Pyrexia	22	3
Fatigue[e]	20	2
Procedural complications		
Infusion-related reactions[f]	21	3
Musculoskeletal and connective tissue disorders		
Arthralgia	12	0
Back pain	11	2
Metabolic and nutritional disorders		
Decreased appetite	12	0
Infections		
Upper respiratory tract infection[g]	11	0

[a] Keratopathy was based on slit lamp eye examination, characterized as corneal epithelium changes with or without symptoms.

[b] Visual acuity changes were determined upon eye examination.

[c] Blurred vision included diplopia, vision blurred, visual acuity reduced, and visual impairment.

[d] Dry eyes included dry eye, ocular discomfort, and eye pruritus.

[e] Fatigue included fatigue and asthenia.

[f] Infusion-related reactions included infusion-related reaction, pyrexia, chills, diarrhea, nausea, asthenia, hypertension, lethargy, tachycardia.

[g] Upper respiratory tract infection included upper respiratory tract infection, nasopharyngitis, rhinovirus infections, and sinusitis.

Clinically relevant adverse reactions in <10% of patients included:

Eye Disorders: Photophobia, eye irritation, infective keratitis, ulcerative keratitis.

Gastrointestinal Disorders: Vomiting.

Infections: Pneumonia.

Investigations: Albuminuria.

Table 2 summarizes the laboratory abnormalities in DREAMM-2.

Table 2. Laboratory Abnormalities (≥20%) Worsening from Baseline in Patients Who Received BLENREP in DREAMM-2

Laboratory Abnormality	BLENREP N = 95	
	All Grades (%)	Grades 3-4 (%)
Hematology		
Platelets decreased	62	21
Lymphocytes decreased	49	22
Hemoglobin decreased	32	18
Neutrophils decreased	28	9
Chemistry		
Aspartate aminotransferase increased	57	2
Albumin decreased	43	4
Glucose increased	38	3
Creatinine increased	28	5
Alkaline phosphatase increased	26	1
Gamma-glutamyl transferase increased	25	5
Creatinine phosphokinase increased	22	1
Sodium decreased	21	2
Potassium decreased	20	2

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

The immunogenicity of BLENREP was evaluated using an electrochemiluminescence (ECL)-based immunoassay to test for anti-belantamab mafodotin antibodies. In clinical studies of BLENREP, 2/274 patients (<1%) tested positive for anti-belantamab mafodotin antibodies after treatment. One of the 2 patients tested positive for neutralizing anti-belantamab mafodotin antibodies following 4 weeks on therapy. Due to the limited number of patients with antibodies against belantamab mafodotin-blmf, no conclusions can be drawn concerning a potential effect of immunogenicity on pharmacokinetics, efficacy, or safety.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, BLENREP can cause fetal harm when administered to a pregnant woman, because it contains a genotoxic compound (the microtubule inhibitor, MMAF) and it targets actively dividing cells *[see Clinical Pharmacology (12.1), Nonclinical Toxicology (13.1) of full Prescribing Information]*. Human immunoglobulin G (IgG) is known to cross the placenta; therefore, belantamab mafodotin-blmf has the potential to be transmitted from the mother to the developing fetus. There are no available data on the use of BLENREP in pregnant women to evaluate for drug-associated risk. No animal reproduction studies were conducted with BLENREP. Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcome. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data: Animal reproductive or developmental toxicity studies were not conducted with belantamab mafodotin-blmf. The cytotoxic component of BLENREP, MMAF, disrupts microtubule function, is genotoxic, and can be toxic to rapidly dividing cells, suggesting it has the potential to cause embryotoxicity and teratogenicity.

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8.2 Lactation

Risk Summary

There is no data on the presence of belantamab mafodotin-blmf in human milk or the effects on the breastfed child or milk production. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with BLENREP and for 3 months after the last dose.

8.3 Females and Males of Reproductive Potential

BLENREP can cause fetal harm when administered to pregnant women *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential prior to initiating BLENREP.

Contraception

Females: Advise women of reproductive potential to use effective contraception during treatment and for 4 months after the last dose.

Males: Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use effective contraception during treatment with BLENREP and for 6 months after the last dose *[see Nonclinical Toxicology (13.1) of full Prescribing Information]*.

Infertility

Based on findings in animal studies, BLENREP may impair fertility in females and males. The effects were not reversible in male rats, but were reversible in female rats *[see Nonclinical Toxicology (13.1) of full Prescribing Information]*.

8.4 Pediatric Use

The safety and effectiveness of BLENREP in pediatric patients have not been established.

8.5 Geriatric Use

Of the 218 patients who received BLENREP in DREAMM-2, 43% were aged 65 to less than 75 years and 17% were aged 75 years and older. Clinical studies of BLENREP did not include sufficient numbers of patients aged 65 and older to determine whether the effectiveness differs compared with that of younger patients. Keratopathy occurred in 80% of patients aged less than 65 years and 73% of patients aged 65 years and older. Among the patients who received BLENREP at the 2.5-mg/kg dose in DREAMM-2 (n = 95), keratopathy occurred in 67% of patients aged less than 65 years and 73% of patients aged 65 years and older. Clinical studies did not include sufficient numbers of patients 75 years and older to determine whether they respond differently compared with younger patients.

8.6 Renal Impairment

No dose adjustment is recommended for patients with mild or moderate renal impairment (estimated glomerular filtration rate [eGFR] 30 to 89 mL/min/1.73 m^2 as estimated by the Modification of Diet in Renal Disease [MDRD] equation) *[see Clinical Pharmacology (12.3) of full Prescribing Information]*. The recommended dosage has not been established in patients with severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2) or end-stage renal disease (ESRD) with eGFR <15 mL/min/1.73 m^2 not on dialysis or requiring dialysis *[see Clinical Pharmacology (12.3) of full Prescribing Information]*.

8.7 Hepatic Impairment

No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin ≤upper limit of normal [ULN] and aspartate aminotransferase (AST) >ULN or total bilirubin 1 to ≤1.5 × ULN and any AST).

The recommended dosage of BLENREP has not been established in patients with moderate or severe hepatic impairment (total bilirubin >1.5 × ULN and any AST) *[see Clinical Pharmacology (12.3) of full Prescribing Information]*.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Ocular Toxicity

- Advise patients that ocular toxicity may occur during treatment with BLENREP *[see Warnings and Precautions (5.1)]*.
- Advise patients to administer preservative-free lubricant eye drops as recommended during treatment and to avoid wearing contact lenses during treatment unless directed by a healthcare professional *[see Dosage and Administration (2.3) of full Prescribing Information, Warnings and Precautions (5.1)]*.
- Advise patients to use caution when driving or operating machinery as BLENREP may adversely affect their vision *[see Warnings and Precautions (5.1)]*.

BLENREP REMS

BLENREP is available only through a restricted program called BLENREP REMS *[see Warnings and Precautions (5.2)]*. Inform the patient of the following notable requirements:

- Patients must complete the enrollment form with their provider.
- Patients must comply with ongoing monitoring for eye exams *[see Warnings and Precautions (5.1)]*.

Thrombocytopenia

- Advise patients to inform their healthcare provider if they develop signs or symptoms of bleeding *[see Warnings and Precautions (5.3)]*.

Infusion-Related Reactions

- Advise patients to immediately report any signs and symptoms of infusion-related reactions to their healthcare provider *[see Warnings and Precautions (5.4)]*.

Embryo-Fetal Toxicity

- Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.5), Use in Specific Populations (8.1, 8.3)]*.
- Advise women of reproductive potential to use highly effective contraception during treatment and for 4 months after the last dose *[see Warnings and Precautions (5.5), Use in Specific Populations (8.3)]*.
- Advise males with female partners of reproductive potential to use effective contraception during treatment with BLENREP and for 6 months after the last dose *[see Use in Specific Populations (8.3), Nonclinical Toxicology (13.1) of full Prescribing Information]*.

Lactation

- Advise women not to breastfeed during treatment with BLENREP and for 3 months after the last dose *[see Use in Specific Populations (8.2)]*.

Infertility

- Advise males and females of reproductive potential that BLENREP may impair fertility *[see Use in Specific Populations (8.3)]*.

Manufactured by:

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For:

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Research Triangle Park, NC 27709

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for injection 100 mg

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Elderly Patients with Newly Diagnosed MM Have Better Outcomes with Triplet Treatment

Rebecca Araujo

Older adults aged >75 years with newly diagnosed multiple myeloma (MM) are more likely to achieve a very good partial response (VGPR), or better, when treated with a triplet combination compared with other therapies, according to a study published recently in *Leukemia & Lymphoma*.[1] Patients in the study who were treated with triplet therapy also achieved prolonged progression-free survival (PFS) and overall survival (OS), The study represents the largest retrospective review of MM patients aged >75 years treated in the "era of novel agents," said the investigators, led by Shaji K. Kumar, MD, consultant in the Division of Hematology, Department of Internal Medicine at the Mayo Clinic, Rochester, MN. .

"Multiple studies have shown that age remains one of the most important prognostic factors in MM, with the outcomes for older patients not having improved to the same degree as that for younger patients over the past two decades," Dr. Kumar told *Multiple Myeloma Today*. "It is important to evaluate the outcomes of older patients, as they are less likely to receive the intense therapies that the younger patients receive nowadays, especially using multiple drug combinations as well as stem cell transplantation," he stressed. However, "studies have shown that older patients may derive similar benefits from multi-drug combinations, such as those used in younger patients, if they are used with adequate dose modifications," he noted.

Retrospective review of Mayo Clinic patients

Dr Kumar and his colleagues retrospectively reviewed data from 394 patients aged >75 years (62% male) with newly diagnosed MM treated at the Mayo Clinic between January 2004

and January 2018. Half the patients had ISS stage 3 disease and 23% had high-risk genetics identified via FISH testing.

The most commonly administered treatment regimen in these patients (31%) consisted of an immunomodulatory drug (IMiD), such as lenalidomide, plus dexamethasone (dex). Other doublet combinations administered were an alkylator, such as melphalan, plus a steroid or other therapy (in 19% of patients), or a proteasome inhibitor (PI), such as bortezomib, plus dexamethasone (10%).

Only 40% of patients received a triplet regimen, most frequently (in 31%) an alkylator (usually cyclophosphamide) plus a PI (bortezomib) plus a steroid (dexamethasone; alkylator-PI-steroid). Other triplet regimens consisted of an IMiD (lenalidomide) plus a PI (bortezomib) plus dexamethasone (IMiD-PI-dex, in 13%) or an alkylator (melphalan) plus an IMiD (lenalidomide) plus a steroid (prednisone; alkylator-IMiD-steroid, in 10%).

Duration of therapy, which varied by regimen, was between 3 and 8 months, less than usually seen in a younger population, the investigators observed, probably due to more comorbidities as well as less bone marrow reserve and more cytopenias in the older patients.

Triplet regimens associated with better outcomes

Among patients who received a triplet regimen, the odds of achieving rVGPR were significantly higher than for patients who received other therapies (46% vs 21%; $P<0.0001$). More than 40% of patients who received IMiD-PI-dex or alkyator-PI-steroid demonstrated VGPR or better, and >20% of patients who received the IMiD-PI-dex regimen achieved a complete response (CR). Among those treated with alkylator-PI-steroid, around 30% achieved VGPR and >40% of patients achieved PR. Among patients who received a doublet regimen, a PR was seen in r30% and over 30% of those who received an IMiD or a PI, plus dexamethasone achieved a VGPR or better. Fewer than 10% of patients who received other therapy regimens achieved a VGPR.

The IMiD-PI-dex and alkylator-PI-steroid regimens were associated with the longest median PFS (36.1 and 30.8 months, respectively) and alkylator-PI-steroid was associated with the longest median OS (55.2 months), Patients who received a triplet combination had better PFS and OS than those on other therapies (30.4 months vs 19.9 months, $P=0.001$), and 50.2 months versus 32.8 months, ($P=0.0006$).

Univariate and multivariate analysis showed that revised (R)-ISS stage <3 was predictive for PFS ($P=0.03$) and OS ($P=0.0003$) and there was a trend toward longer PFS for use of a triplet regimen ($P=0.05$). Receiving a triplet combination and having bone marrow plasma cell percentage (BMP) <60% were predictive for OS ($P=0.02$ and $P=0.03$, respectively).

Results not unexpected but informative

The results of this study were not surprising, Dr. Kumar admitted. "As we had expected, we found better outcomes amongst the patients who were treated with multi-drug combinations," he said. However, the new data "give us perspective on what we need to focus on in order to improve outcomes for these patients."

The study was limited by its retrospective nature, which prevents further analysis on factors surrounding treatment selection. "Unfortunately, the current study does not clearly tell us why some older patients were started on multi-drug combinations while the others were treated with the two drug combinations," Dr. Kumar commented. Another limitation was the lack of available toxicity data.

Looking to future areas of exploration based on these results, "prospective trials have to be designed to enroll these older patients with introduction of newer therapies and with careful attention paid to toxicity and the quality of life," he said. "This will enhance our understanding of the optimal approach for these patients." These findings emphasize the importance of "constantly reevaluating the older patients to see if the therapy can be intensified along the way."

Current challenges in elderly MM patients

Despite the benefit, certain challenges persist in using intensive therapy in this population, Dr. Kumar stressed. "Increased toxicity is the major concern treating these patients with the three-drug combinations," Dr Kumar cautioned. "In addition, because of comorbidities, many of these patients are often on other drugs that can interact with the drugs that are used for treatment of MM and may also enhance their toxicity profile."

To safely increase the intensity of therapy in patients with advanced age, Dr Kumar suggests that "a reasonable approach would be to start these older patients on less intense therapies and then increase the intensity of therapy or add the third drug to the two-drug combination as the tolerability is better ascertained and overall functional status improves with the initial disease control." This approach "must be balanced with the disease aggressiveness, where high-risk disease should probably be treated with a more intense approach right in the beginning so as not to lose control of the disease."

"Pay careful attention to drug–drug interactions when these patients are started on new myeloma drugs as well as other supportive care therapies," Dr Kumar urges. "Careful attention to the supportive care management is very important for these older patients and can go a long way in terms of improving their outcomes." ■

Rebecca Araujo is a medical writer for *Docwire News*.

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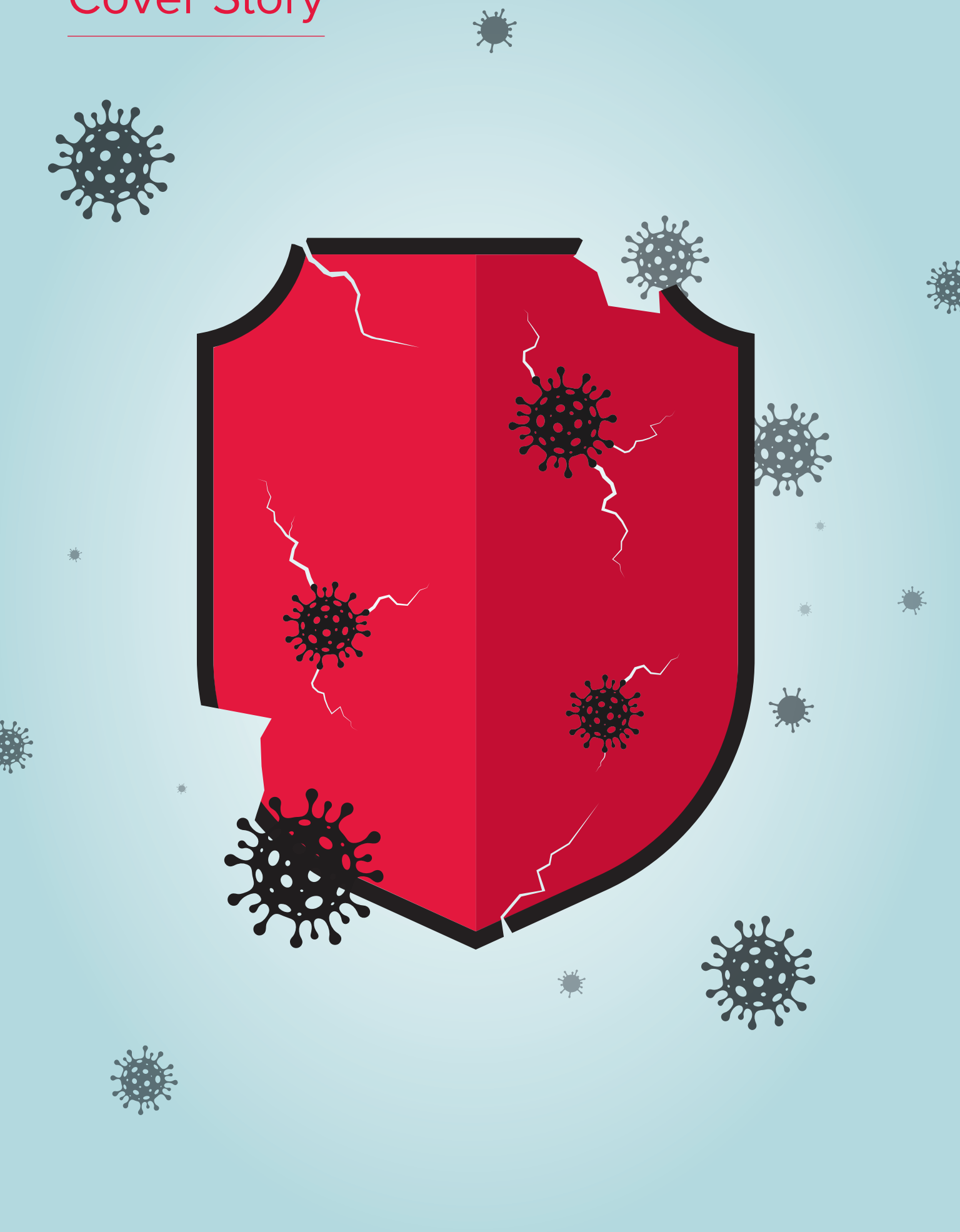
Cover Story



Response to mRNA COVID-19 vaccines in patients with multiple myeloma

Interview with James R. Berenson, MD, President, Institute for Myeloma & Bone Cancer Research (IMBCR); Berenson Cancer Center West Hollywood, CA

Vanessa Ira

Multiple myeloma patients are known to be at higher risk for severe coronavirus disease 19 (COVID-19) infection. However, little has been known about responses to COVID-19 vaccination in multiple myeloma patients since anyone with an active malignancy was excluded from pivotal clinical trials with the vaccines. An observational study recently published in the journal *Leukemia,* of multiple myeloma patients, investigated their response to double vaccination with one of the currently available mRNA vaccines, BNT162b2 (Comirnaty, Pfizer-BioNTech) or mRNA-1273 (Moderna COVID-19 Vaccine, Moderna). Response was measured by an ELISA-based assay that detected immunoglobulin (Ig) G antibodies to the spike protein of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Based on this test, investigators found that only 45% of 96 patients with active multiple myeloma achieved an adequate response to the vaccine compared with 94% of 31 age-matched healthy subjects. Although the two mRNA vaccines encode nearly identical products, patients vaccinated with mRNA-1273 achieved higher COVID-19 antibody levels than those vaccinated with BNT162b2, suggesting that mRNA 1273 might be the preferred vaccine option for patients with active myeloma, the investigators suggested. Patients who do not respond to either of these vaccines remain at high risk and should be considered for prophylactic infusions of anti-SARS-CoV-2 monoclonal antibodies or intermittent immunoglobulin infusions, they advised.

Multiple Myeloma Today spoke with James R. Berenson, MD, senior investigator on the study[1], about its implications for multiple myeloma patients. Dr Berenson has specialized in the treatment of patients with multiple myeloma, monoclonal gammopathy of undetermined significance (MGUS), amyloidosis, Waldenström's macroglobulinemia, and metastatic bone disease, as well as conducting research related to these diseases, both in the basic and clinical areas for more than 30 years. In addition to his oncology practice in West Hollywood, Dr Berenson serves as President of the Institute for Myeloma & Bone Cancer Research (IMBCR) and CEO of Oncotherapeutics. Dr. Berenson has published numerous articles in top scientific and medical journals related to his work.

MM Today: **Why are multiple myeloma patients at higher risk for severe COVID-19?**

Dr James Berenson: Myeloma patients lack a competent immune system and, thus, are at higher risk to develop COVID-19 infection, and they experience a more severe form of the disease. They lack a proper immune functioning B-cell population because of their underlying disease, and many of the treatments target not only the malignant B-cells, but the normal ones as well. That's because the cancer cell in myeloma is a type of B-cell. So, we're getting rid of the tumor cell with these targeted-antibody treatments, but, unfortunately, we're also doing a lot of collateral damage to normal immune B-cells that are important in achieving an antibody response to the COVID-19 mRNA vaccine. As a result, myeloma patients don't respond as well. We've known for a long time that myeloma patients contract more infections, and they also don't respond to other types of vaccines. This is due to their normal low antibody levels, but also, they have what we call impaired T-cell responses, which is important in the immune response to a COVID-19 infection and its vaccines. So, these patients have more viral infections, and COVID-19 obviously is one of those viruses that they are more susceptible to contracting.

What were some of the factors associated with low response to mRNA vaccines in this group?

That's a great question. We went through all the usual factors that have been identified from previous vaccination studies in this population, for example, with flu, pneumococcal and shingles vaccines. Our results were quite consistent with those

studies. So, patients who had poor responses to the mRNA COVID-19 vaccines were older and had poor kidney function. Those who were on salvage therapy, in other words who had failed their first-line therapy, and those whose myeloma was not under control, did more poorly with the vaccinations.

The patient's underlying immune function also predicted their outcomes, so that those with lower lymphocyte counts or reduced levels of normal antibodies showed impaired responses to vaccination. For example, if the patient had an IgG myeloma, and then we measured their normal antibodies, which would be IgM and IgA, if they were low, these people did not respond well to vaccination.

Thus, we identified a number of specific factors that identified the likelihood of response to the vaccines. The most important one was that patients who received the Moderna mRNA-1273 vaccine were much more likely to respond than those who received the Pfizer BNT162b2 vaccine. The average response to mRNA-1273 was nearly 3.5- fold higher in terms of levels of antibody in the blood against the spike COVID-19 protein compared with BNT162b2. Looking at the proportion of patients who responded fully, it was nearly two-thirds of patients vaccinated with mRNA-1273, but only one-third of those who received the BNT162b2 vaccine.

MYELOMA PATIENTS CONTRACT MORE INFECTIONS, AND THEY ALSO DON'T RESPOND TO OTHER TYPES OF VACCINES. THIS IS DUE TO THEIR NORMAL LOW ANTIBODY LEVELS, BUT ALSO, THEY HAVE WHAT WE CALL IMPAIRED T-CELL RESPONSES, WHICH IS IMPORTANT IN THE IMMUNE RESPONSE TO A COVID-19 INFECTION AND ITS VACCINES.

What were the limitations of the study?

The limitation was the number of patients, because one of the things we wanted to do is see whether we could identify specific drugs that may be more likely to either give you a good response or poor response to vaccination. We did identify having taken steroids as predicting an impaired response, but that was predictable because these drugs are immunosuppressive. There is a study[2] from the group at Mount Sinai that, as we would predict, some of the antibody treatments that not only target the malignant plasma cell, but also indiscriminately knock off normal plasma cells that are the antibody-producing cells in your body are associated with lower response rates.

What are the clinical implications of your findings for patients with multiple myeloma?

If you looked at all the patients in our study, among those who had active myeloma, i.e., those who were requiring treatment, only about 45% had a good response and about one-third had no response, and about one-quarter had a diminished response. So, there are a lot of these patients who are not responding enough to probably ward off the virus, and they don't really know that, because they're not getting these COVID-19 antibody response tests. If you look at a normal population, the proportion that has a diminished response is only about 5% and none in our study had no response at all.

With the continuation of the COVID-19 pandemic, what are the advances you foresee in vaccination for multiple myeloma patients?

We're now coming to the point of suggesting booster vaccination, which we should probably call revaccination strategies for myeloma patients. I do think that it's going to be warranted. The problem is – and this is important for people to understand - the measurement of the antibody response is only accurate for the first 2-3 weeks after the vaccine has been administered. After that, the antibody levels decrease in all of us, after only a couple of months. It is because you no longer have the COVID-19 spike protein around to stimulate the normal plasma cells to make antibodies to COVID-19. Specifically, the mRNA in the vaccine is turned into spike protein. After several weeks, however, that spike protein goes away because the mRNA is no longer present to be able to make the spike protein, so the antibodies against COVID-19 are no longer able to be made by the normal plasma cells. However, that doesn't mean you are not protected, because of what we know now from another study[3]. Among people who had COVID-19 infection, if you study their bone marrow where the plasma cells are, those antibody-producing cells are still around, but they're dormant. But if you get COVID-19 infection, they can wake up and produce antibodies to fight off the infection. So, it's really complicated at this point to determine exactly when people need to have revaccinations. But in general, I think myeloma patients are going to need them. ■

Vanessa Ira is the managing editor of *Multiple Myeloma Today*.

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Present-day Challenges in the Treatment of Multiple Myeloma

Brandon May

Participants

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Several challenges exist in the management of multiple myeloma (MM) today, due to the genetic complexity and instability of the disease, and, lately, the coronavirus disease 2019 (COVID-19) pandemic. In a series of virtual discussions held on August 6, 2021, four specialists in the field of multiple myeloma discussed some of the real-world challenges they face the current care of patients.

Treatment selection in newly diagnosed patients

"My approach has really evolved during the past year," declared Dr Krishan, explaining that as well as selecting treatments associated with high response rates, he is gravitating increasingly toward pushing for patients to achieve minimal residual disease (MRD) negativity. "With that in mind, I started to be more aggressive about adopting a quadruplet regimen, perhaps not initially, but certainly if I'm not going to do daratumumab plus RVd [lenalidomide, bortezomib, and dexamethasone], I may do it quickly after one or two cycles if I'm not happy with the depth or speed of response," she said. Other patients, especially higher-risk young patients, will get a quadruplet regimen from the start, she added. Dr Lu agreed that MRD status can offer significant prognostic implications in multiple myeloma. "I think it can be very important as achieving MRD negativity can be associated with… favorable patient outcomes," he said. He emphasized the importance of using aggressive therapy "to try to drive the patient quickly to MRD negativity, both in terms of the number of drugs used, as well as the tempo."

According to Dr Kumar, in transplant-eligible patients, the typical treatment approach should be to use a three-drug combination regimen consisting of a proteasome inhibitor, an immunomodulatory drug (IMiD), and a steroid. For patients with high-risk MM based on cytogenetic abnormalities, a four-drug combination, with the addition of a CD38-targeting drug, would be the usual approach, he stated. For transplant-ineligible patients, a typical treatment regimen would consist of a monoclonal antibody, an IMiD, and a steroid, or a proteasome inhibitor, an IMiD, and a steroid, depending on the patient's ability to tolerate a triplet regimen, Dr Kumar added. If these patients fail that regimen, he suggested that a doublet may be given with the third drug added; when the patient's condition improves, they can be seen to tolerate it.

DR USMANI CONCLUDED THAT THE MOST IMPORTANT CONSIDERATION IS TO WORK TOWARD INITIATING THE BEST THERAPIES TO ENSURE PATIENTS ACHIEVE THE BEST RESPONSE WITHOUT CHANGING TREATMENTS IN AN EFFORT OBTAIN A DEEPER RESPONSE.

The most important consideration is to work toward initiating the best therapies to ensure patients achieve the best response without changing treatments in an effort obtain a deeper response, Dr Usmani concluded. "The idea would be to pick the best treatment option that gives the patient the best chance of getting to MRD negativity during that first year," he stressed.

Treating relapsed/refractory multiple myeloma

"When we talk about relapsed disease, we now have a lot more variables that we can take into account when we decide on treatment," Dr Kumar noted. One of the most important is the patient's ability to tolerate a particular regimen. Importantly, "at that point the clinician will have information on what drugs the patient is refractory to, so we want to try and introduce different drug classes," he emphasized. Physicians should also consider the duration of the first response, given this can be a critical measure of disease risk, he added. "Then, of course, we want to take into account the logistics of administration, patient preferences, and so forth."

For Dr Krishnan, an easy way to approach relapse is to remember the "4 Ts" – timing (of relapse), transplant, treatment, and toxicity. With respect to timing of relapse, "Dr. Kumar's work has clearly shown that if you relapse within a year after your transplant, that's a very poor risk factor," she noted. In patients who elected to defer transplant, clinicians should consider doing a transplant at first relapse. Dr Krishnan stressed the importance of considering patients' treatment prior to transplant, which becomes "more challenging as we are using quadruplets early on in the course of disease."

Exposure to a regimen doesn't necessarily mean that the patient is refractory to it, she pointed out. "For example, if a patient has a quadruplet induction and transplant and then relapses on lenalidomide maintenance, that does not mean that the patient it refractory to some of those drugs used initially," she stressed

Regarding toxicity, Dr. Krishnan noted that this concern grows as more increasingly potent drugs become available. "We do need to keep that in mind, because quality of life is important...I think we're going to touch on that in terms of patient-reported outcomes," she predicted.

COVID-19 in the multiple myeloma patient

The global COVID-19 pandemic has caused major disruptions in healthcare and complicated the management of patients with all malignancies. Patients with multiple myeloma are immunosuppressed, which places them at high risk for severe complications and morbidity from COVID-19 infection. Older age (r65 years) in most patients is also a significant risk for adverse outcomes.

As the pandemic continues, healthcare providers have sought to avoid unnecessary contact with patients to minimize exposure and their risk of infection. "A lot of physicians have tried to move away from regimens that require a lot of clinic or infusion suite visits wherever possible," Dr Lu acknowledged. Both Dr Lu and Dr Kumar described how most transplant-eligible patients, especially those whose disease was under good control, had their transplant deferred. "We did convert to oral therapy wherever possible, especially in patients with stable disease on maintenance phase," Dr Kumar said, adding that patients with active disease continued on appropriate therapy based on "the understanding that controlling the disease is probably most important at that time."

> **"A LOT OF PHYSICIANS HAVE TRIED TO MOVE AWAY FROM REGIMENS THAT REQUIRE A LOT OF CLINIC OR INFUSION SUITE VISITS WHEREVER POSSIBLE."**
>
> **– DR LU**

For patients with multiple myeloma, like those with many other conditions, their interactions with healthcare providers have been shifted from face-to-face, in-office visits to virtual telehealth consultations using mobile apps. From his own experience, Dr Lu recalled that many physicians have tried to move away from regimens that require a lot of clinic or infusion suite visits whenever possible. Dr Kumar described how "we tried to do a lot more virtual visits and then have patients go to nearby clinics to do the blood work so that they could avoid the travel, and they would send us either the results, or we would send a kit for them to send the blood back to the lab for us to do the blood work."

Dr Krishnan acknowledged that, especially in a geographically large state like California, telehealth "has really saved many of our patients hours of travel for routine follow-up visits." Following blood counts and monitoring side effects can be done by telehealth, she noted.

"The COVID-19 pandemic certainly accelerated the whole concept of virtual medicine," Dr Kumar acknowledged. "In regard to telehealth, I think that it is here to stay," Dr Krishnan declared. Dr Usmani agreed: "We are recognizing that there were a lot of positives that we learned from that experience that we'd like to retain," he conceded. ■

Brandon May is a freelance medical writer.

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Black Patients with Multiple Myeloma Have More Severe Complications, but Receive Less Care

Rebecca Araujo

Two recently published studies discuss racial disparities in the care and treatment of patients with multiple myeloma (MM) in the US. According to the results of one study, Black and Hispanic patients with MM are more likely to be hospitalized due to MM-related complications, but less likely to receive standard treatments and care, such as palliative care consultations, than white patients.[1] A second study confirmed that palliative radiotherapy is less frequently administered to Black MM patients within one year of diagnosis or at the end of life compared with non-Hispanic white patients, which supports previous findings that pain and other symptoms are not adequately addressed in Black patients.[2] Both studies appeared in the journal *Leukemia & Lymphoma*.

MM-related hospitalization

In the first published study, researchers from Baylor College of Medicine, Houston, and other centers in Texas, Arkansas, and North Carolina, examined whether previously identified gaps in care for MM between different racial/ethnic groups were decreasing. Trends in MM-related hospitalizations and all-cause in-hospital mortality among patients who identified as Hispanic, non-Hispanic white, or non-Hispanic Black were identified via 2008-2017 records from the Nationwide Inpatient Sample (NIS), the all-payer hospital inpatient care database produced by the Healthcare Cost and Utilization Project (HCUP).

During this 10-year study period, the prevalence of MM-related hospitalizations in non-Hispanic Black patients was 476 per 100,000, significantly higher than the prevalence among non-Hispanic white patients (305.6 per 100,000; $P<0.001$). The most frequent reason cited for hospitalization in non-Hispanic Black patients was acute renal failure, whereas for the other groups the reason was pneumonia.

Race and ethnicity were associated with rates of MM-related in-hospital mortality. For Hispanic patients, in-hospital mortality was 6.2%, compared to an average of 5.3% among non-Hispanic Black and white patients ($P<0.001$).

In-hospital management of multiple myeloma

Despite the higher rate of hospitalization seen for non-Hispanic Black MM patients, the study investigators found that well-established and effective MM therapies

were less often utilized in these patients compared with Hispanic and non-Hispanic white patients. Non-Hispanic Black patients received autologous stem cell transplantation (ASCT), a standard of care in MM, less often than non-Hispanic white patients (2.8% vs 3.8%, respectively). Black patients also received fewer palliative care consultations and less chemotherapy. Black patients received more in-patient blood product transfusions and more intensive care than non-Hispanic white patients, likely reflecting their higher disease burden as well as poorer outpatient disease control, the investigators noted.

Both non-Hispanic Black and Hispanic patients had longer hospital stays than non-Hispanic white patients. Mean costs of hospitalization were higher in both groups compared with non-Hispanic white patients, a "striking" finding for Black patients, who had comparatively decreased treatment with chemotherapy and expensive ASCT, the investigators pointed out. Costs were highest for Hispanics, who received the greatest number of ASCTs and the most chemotherapy.

Average annual percent change (AAPC) analysis revealed a statistically significant decline in overall in-hospital mortality among patients with MM during the study period, although, notably, this improvement in mortality was not seen in Black patients, who demonstrated the highest rates of in-patient mortality (AAPC, –2.2, 95% confidence interval –4.7-0.4).

From their findings, the researchers concluded that, "disparities in MM care for non-Hispanic Black [patients] and Hispanic [patients] continue to persist despite recent advancements in MM therapy."

Disparities in palliative radiotherapy

In the second study, researchers from the University of Southern California Keck School of Medicine, Los Angeles, sought to determine whether racial or ethnic differences existed in the use of palliative radiotherapy in MM. Palliative radiotherapy is a standard of care for painful bone metastases associated with MM. Inadequate management of pain has previously been reported in Black patients in many other healthcare settings, the California investigators noted.

For their analysis, the investigators utilized the National Cancer Database, a registry estimated to hold data on 70% of malignancies diagnosed throughout the US. They identified 173,556 patients diagnosed with MM between 2004 and 2016, of whom about 20% were Black. Among the MM patients overall, 13.7% received palliative radiotherapy, defined as a total dose of 4-30 Gy of radiation within one year of MM diagnosis. Among different racial/ethnic groups with diagnosed MM, palliative radiotherapy was administered in 15.5% of non-Hispanic white patients, 15.8% of Hispanic patients, and 14.3% of Black MM patients.

"Despite this relatively small absolute difference in radiotherapy use, we believe these findings are clinically significant in the context of an MM landscape permeated by known racial disparities in treatment and outcomes," the researchers commented.

Black patients were found to be 13% less likely to receive radiotherapy within the first year of diagnosis compared to white patients (P<0.0001). Decreased receipt of radiation was also associated with older age, female sex, higher comorbidity score, living more than 12.5 miles from the treatment facility, having Medicare or private insurance, and living in areas with the highest median income bracket. Some of these factors could explain in part why Black patients receive palliative radiotherapy less often, the researchers suggested. Increased odds of receiving radiation therapy were associated with living in an urban or rural community (versus a metro community), having other government insurance, and previous receipt of chemotherapy.

The study also found that compared with non-Hispanic white patients, Black patients were 18% less likely to die within 30 days of initiating palliative radiotherapy (P=0.046) suggesting "a decreased tendency to treat these patients at the end of life."

According to the investigators, the decreased use of palliative radiotherapy in Black patients could be in part due to "inaccurate perceptions of pain, suspicion of opioid-seeking behavior, and incorrect beliefs that [Black] patients experience pain differently from non-Hispanic white patients and have a higher pain tolerance." Miscommunication and unconscious bias among providers could also be factors.

Addressing racial disparities

Disparities in care may lead to further differences in outcomes and survival. Identifying areas where improvements can be made to offer equitable care may help to address the gap in outcomes between Black patients and their white counterparts. Further research is needed to illuminate the mechanisms behind these disparities to eliminate them in MM care, but also healthcare at large. Overall, "urgent changes in the health care systems and targeted interventions" are needed, say the Baylor researchers.

Rebecca Araujo is a medical writer for *Docwire News*.

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IN THIS SECTION

For a sneak peek into the next issue, take a look at the online version of the **Virtual Roundtable Discussion Part II:** a conversation between our Editor-In-Chief, **Dr. Saad Usmani,** The Leukemia & Lymphoma Society, **and two myeloma survivors and patient advocates.**

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T-CELL REDIRECTING BISPECIFIC ANTIBODIES FOR THE TREATMENT OF MULTIPLE MYELOMA

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Introduction

Multiple myeloma (MM) patients who develop disease refractory to immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs), and CD38-targeting antibodies (triple-class refractory disease) have a poor outcome and an as yet unmet medical need for new effective therapies. The LocoMMotion study is providing real-world data on outcomes in triple-class exposed MM patients receiving standard-of-care therapies. The first analysis of this prospective study showed that triple-class exposed patients (74% triple-class refractory) had an overall response rate (ORR) of only 20% with standard-of-care salvage therapies.[1] Similarly, the MAMMOTH study, which retrospectively investigated the clinical outcomes of patients refractory to CD38 antibodies, showed a median overall survival of <12 months for triple-class refractory patients, and 5.6 months for penta-refractory patients (disease refractory to 2 IMiDs, 2 PIs, and CD38 antibodies).[2] This clearly indicates that new agents with a novel mechanism of action are needed to treat these patients. Promising in this respect are the different T-cell redirecting therapies currently under investigation in heavily pretreated MM patients.

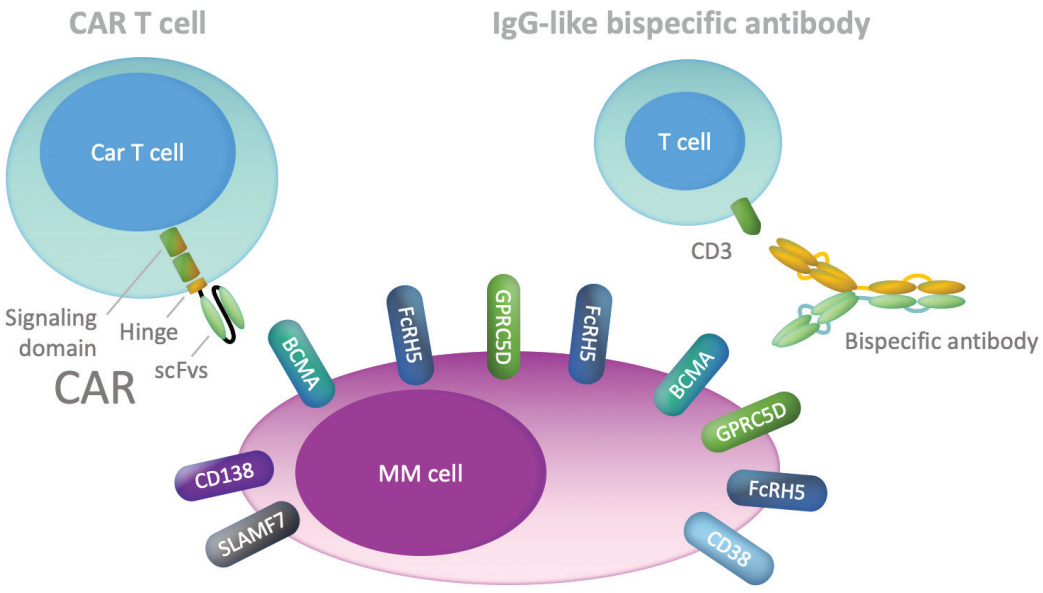
Niels W.C.J. van de Donk, MD, PhD

Bispecific antibodies

T-cell redirecting bispecific antibodies (BsAbs) have the ability to simultaneously target CD3 on the T-cell surface and a tumor-associated antigen on the tumor cell surface (**Figure**). This results in the formation of an immune synapse and subsequent release of granzymes and perforins, resulting in lysis of the tumor cell.[3] A big advantage of BsAbs is that these agents are available directly "off-the-shelf," which is especially important for patients with rapidly progressing disease.[4] There are different BsAb formats, with two BsAb classes predominantly evaluated in clinical trials. These include IgG-like BsAbs and bispecific T-cell engagers (BiTEs), which consist of two single-chain variable fragment (scFv) units fused with a short flexible linker. Because of their small size, BiTEs need to be administered via continuous infusion, while the IgG-like BsAbs can be given via intermittent intravenous or subcutaneous dosing, which is more convenient for patients.

B-cell maturation antigen (BCMA) is the target of several BCMA-specific BsAbs, because of its restrictive expression pattern, and thereby low risk for "on target/off tumor" toxicities. BCMA is expressed only on normal plasma cells and a subset of mature B-cells, as well as on MM cells. Pacanalotamab (formerly AMG 420), the first-in-class BCMA-specific BiTE molecule, was evaluated in heavily pretreated patients with a median of 5 prior lines of therapy. The ORR at the maximum tolerated dose was 70% (7 of 10 patients), which included minimal residual disease (MRD)-negative complete response (CR) in 50%.[5] Development of pacanalotamab was stopped, however, because of the need for continuous infusion. A study with a half-life extended BiTE molecule, pavurutamab (formerly AMG 701), administered as weekly intravenous infusion, is ongoing, with an ORR of 83% in the most recently reported cohort.[6]

Figure: T-cells can be redirected to MM cells by using a bispecifc antibody, which simultaneously binds to CD3 and a MM-associated antigen, or by transducing T-cells with a chimeric antigen receptor (CAR). Figure adapted from Verkleij CPM et al.[3]



Adapted by author[3]

Among other BCMA-targeting BsAbs under evaluation in heavily pretreated MM, the most advanced in terms of clinical testing is teclistamab.[7] Teclistamab is an IgG-like antibody that was shown to effectively eliminate BCMA-positive MM cell lines and primary MM cells in in vitro assays, accompanied by T-cell activation and degranulation.[8] Teclistamab was also effective in MM mouse models.[9] Based on these preclinical results, the MajesTEC-1 study was initiated, which to date has administered teclistamabin to a total of 157 patients, intravenously in 84 and subcutaneously in 73.[7] The recommended phase 2 dose (RP2D) was defined as teclistamab 1500 µg/kg administered subcutaneously after two step-up doses to mitigate cytokine-release syndrome (CRS). In the most recent report of the study, 40 patients were treated at the RP2D (median of 5 prior lines of therapy and 83% triple-class refractory). Teclistamab was well tolerated with no new safety signals. Hematologic toxicity occurred mainly during the first and second treatment cycles. The most common non-hematologic adverse event was CRS (70% of patients), which occurred a median of 1 day after injection, and did not reach grade ≥3, and did not lead to treatment discontinuation in any patient. The ORR in patients treated at the RP2D was 65%, including very good partial response (VGPR) or better in 58% and CR or better in 40%. Responses were durable with the RP2D; 85% of responders were alive and continuing on treatment after a median follow-up of 7.1 months.[7]

Elranatamab (formerly PF-06863135), another BCMA-targeting BsAb, was initially evaluated as an intravenous infusion, but in the phase 1 study (MagnetisMM-1) update, presented at the 2021 annual meetings of the European Hematology Association (EHA)[10] and the American Society of Clinical Oncology (ASCO),[11] it was administered subcutaneously in 30 patients (86.7% triple-class refractory). At the RP2D (1000 µg/kg) the overall response rate was 83.3% (n=6 patients). Responses were also reported in patients who were previously exposed to BCMA-targeted therapies. The most common adverse events were again hematologic toxicity and CRS. Preliminary results from several other BCMA-targeting BsAbs, including CC-93269 (alnuctamab),[12] REGN5458,[13] and TNB-383B,[14] have also shown promising response rates with CRS as the most common adverse event.

Recently it was reported that BCMA loss may be a mechanism of acquired resistance to BCMA-bispecifics.[15] Although it is not known how often

> BsAbs are promising new agents that harness the power of T cells to eliminate MM cells.

this occurs, this case report highlighted the importance of identifying new MM-associated antigens for T-cell redirection therapy. In this respect, T-cell redirecting antibodies targeting GPRC5D or FcRH5 are promising in terms of activity and safety. GPRC5D is a protein that is highly expressed on plasma and myeloma cell surfaces, and also on cells that produce keratin.[16,17] Talquetamab is the first-in-class GPRC5D-specific T-cell redirecting BsAb that was shown to eliminate MM cells in different preclinical assays.[16,18,19] An update from the phase 1 MonumenTAL-1 study showed that at the time of data cut-off a total of 184 patients were enrolled (102 received intravenous dosing and 82 subcutaneous dosing).[18] The RP2D for talquetamab has now been determined as 405 µg/kg administered subcutaneously. Toxicities again include hematologic toxicity and CRS, but also, uniquely to GPRC5D targeting with talquetamab, skin toxicity and dysgeusia (probably related to GPRC5D expression in these tissues). These toxicities were effectively managed with supportive care. Talquetamab was active in these heavily pretreated patients (approximately 80% triple-class refractory) with an ORR of 70% with VGPR or better, in 60% of the 30 patients treated at the RP2D.

FcRH5, another myeloma-associated antigen, forms the target for cevostamab.[20,21] As well as normal and malignant plasma cells, FcRH5 is also expressed on B cells.[21] The ORR with cevostamab at the 3.6/20 mg dose level was 53%.[20] A recent update presented at EHA 2021 showed that response to cevostamab was consistent regardless of previous therapies.[20] FcRH5 expression was also not altered by the number of prior lines and or types of prior therapy.

These different BsAbs are in further development as monotherapy and some of these new agents also in combination with other anti-MM agents, such as CD38 antibodies or IMiDs, to further improve depth and duration of response. In addition, an ongoing study (NCT04586426) is also evaluating the combination of teclistamab and talquetamab in RRMM. Dual antigen targeting may prevent development of antigen escape and thereby potentially improve durability of response. Studies with BsAbs are also planned in patients with newly diagnosed MM or with early relapse.

Conclusion

BsAbs are promising new agents that harness the power of T cells to eliminate MM cells. Recent data demonstrated that these novel therapies for the treatment of MM patients show a beneficial balance between activity and toxicity. Ongoing trials will answer several outstanding questions, such as how to best sequence these new T-cell redirecting therapies and which patients will experience most benefit from them.

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TARGETING DEPENDENCE ON THE B-CELL LYMPHOMA 2 (Bcl-2) FAMILY IN MULTIPLE MYELOMA

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Resisting programmed cell death (apoptosis) is one of the many necessary events for the development of cancer.[1] It is required to overcome the pro-death signals triggered by other tumorigenic events such as inappropriate proliferation through dysregulation of oncogenes or loss of tumor suppressor genes.[2] The primary mechanism by which oncogenic stress induces apoptosis is through the induction/activation of pro-apoptotic members of the B-cell lymphoma (Bcl)-2 family.[3] For cells to survive such signals, these pro-apoptotic molecules must be neutralized through upregulation and binding of the anti-apoptotic Bcl-2 proteins, e.g. Bcl-2, B cell lymphoma-extra-large (BCL-XL), and myeloid cell leukemia 1 (Mcl-1).[3] This neutralization comes at a cost, however, leaving cancer cells more dependent on anti-apoptotic BCL2 family members than normal cells.[4] This makes the anti-apoptotic Bcl-2 family members attractive therapeutic targets, since normal adult tissues do not experience similar stress.

Inhibiting the Bcl-2 proteins, however, proved to be a major challenge that resulted in a nearly 30-year journey from the discovery of Bcl-2 in the 1980s to regulatory approval of the first Bcl-2 inhibitor, venetoclax (formerly ABT-199), for treatment of relapsed chronic lymphocytic leukemia with 17p deletion, by the US Food and Drug Administration (FDA) in 2016.[5] Venetoclax was derived from a Bcl-2/Bcl-xL inhibitor, navitoclax (ABT-263), an orally available version of the initial tool compound ABT-737.[6] These drugs function similarly by binding to a groove in the anti-apoptotic proteins, freeing the pro-apoptotic Bcl-2 family members, thus allowing them to induce apoptosis. In myeloma, both Bcl-2 inhibitors and Mcl-1 inhibitors have emerged as promising therapeutic agents.

Martine Amiot, PhD and colleagues at the University of Nantes were the first to demonstrate that a subset of myeloma cell lines harboring the t(11;14) translocation was exquisitely sensitive to ABT-737.[7] Based on gene expression, they concluded that the sensitivity was more likely due to Bcl-2 dependence and went on to demonstrate this, using both BH3-profiling and venetoclax sensitivity.[8,9] These studies provided the rationale for clinical testing of venetoclax in myeloma.

Clinical development of venetoclax in multiple myeloma

While the initial phase 1 study of venetoclax monotherapy study was not designed to specifically test t(11;14) myeloma, nearly all the responses were in t(11;14)-positive patients, where the response rate was 40% compared with only 6% of the t(11;14)-negative population.[10] Importantly, responses were associated with high Bcl-2/Bcl-xL (BCL2L1) ratios, providing a potential prognostic biomarker. Toxicity was minimal in this study. Based on a preclinical study that demonstrated that dexamethasone could synergize with venetoclax in cell lines and patient samples,[11] an expansion cohort of this trial was opened with t(11;14)-positive myeloma using this combination. The response rate increased to 60%, although in the subsequent phase 2 study, consisting of more heavily pretreated and daratumumab-exposed patients, the response rate was lower.[12]

In parallel with the venetoclax monotherapy phase 1 study, a second phase 1 trial was completed in patients with relapsed/refractory multiple myeloma who received the combination of venetoclax with bortezomib and dexamethasone.[13]

The rationale for this combination was data demonstrating that bortezomib induced expression of the pro-apoptotic protein NOXA, which functions by specifically inhibiting Mcl-1. This suggested that inhibiting two anti-apoptotic Bcl-2 family members could have synergistic activity. Indeed, in this trial, the response rate was 67%[13] and this led to a phase 3 study (BELLINI) that compared venetoclax-bortezomib-dexamethasone with bortezomib-dexamethasone.[14]

In the BELLINI trial there was a marked difference in progression-free survival (PFS, 22.4 vs 11.5 months, respectively). Unfortunately, this did not translate into an increase in overall survival (OS), which was initially lower in the venetoclax-containing arm due to early deaths associated with infections and disease progression. While it remains unclear why this happened, the addition of antibiotic prophylaxis and the requirement for non-venetoclax-containing control arms for combination studies were put in place. Combinations with daratumumab and venetoclax-dexamethasone and daratumumab with venetoclax-bortezomib-dexamethasone were recently shown to be highly effective in daratumumab-naïve t(11;14)-positive patients and unselected respectively.[15] Importantly, there was only 1 treatment-emergent death in this trial.

Predictive biomarkers of sensitivity to venetoclax

Together, these studies demonstrate the potential for use of venetoclax in multiple myeloma therapy, but they also point to the need for predictive biomarkers. t(11;14) remains a potential marker, although only about half of these patients responded to monotherapy and both preclinical and clinical studies demonstrated that others may also benefit. BCL2/BCL2L1 ratios also have value, although these are most predictive when the ratio is high and determining the optimal cutoff will require additional studies. Moreover, both protein and mRNA quantification have been used in the clinical trials and each of these will have their challenges for use outside a clinical trial.

Functional profiling has also proven to be an accurate measure of sensitivity, either through BH3-profiling[9] or ex vivo sensitivity testing,[16,17] but these also have limitations as they are not easily performed in clinical laboratories. A recent report demonstrated that venetoclax-sensitive cell lines and patient samples express B-cell markers, consistent with the CD2 subset of myeloma initially identified in the UAMS classification.[18] This opens up the potential of using a flow cytometry panel to identify venetoclax-sensitive patients.

Mcl-1 as potential target in multiple myeloma

While targeting Bcl-2 will likely benefit a specific population of myeloma patients, Mcl-1 appears to be the primary family member on which myeloma cells are dependent and they are therefore a potentially more productive target.[19] Additionally, the MCL1 locus is found at chromosome 1q21, a region of frequent gain or amplification in multiple myeloma, resulting in increased Mcl-1 expression.[20] Several potent and selective Mcl-1 inhibitors have been developed and are currently in clinical trials,[21] although early genetic studies in mice suggested that on-target cardiotoxicity could limit use.[22] For instance, a phase 1 trial with oral MCL-1 inhibitor murizatoclax (AMG 397) was paused because one patient had high serum troponin C, a marker of cardiotoxicity.[23] Thus, considerations for dosing and patient selection (e.g. 1q gain)[24] may be necessary for Mcl-1 inhibitor development.

Targeting key proteins – future directions

Targeting key proteins that myeloma cells are dependent on for survival, such as Bcl-2 and Mcl-1, holds great promise, even in a disease where there are many active therapeutic options. However, understanding how Bcl-2 family proteins function in multiple myeloma, as well as finding accurate predictive biomarkers, holds the key to how to overcome challenges with combination therapies and on-target toxicities.

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ASSIGNING RISK BASED ON 17p DELETION IN MULTIPLE MYELOMA – NOT AS SIMPLE AS IT FIRST SEEMS

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At first glance, it seems very simple: the presence of a deletion of the short arm of chromosome 17 (del[17p]) confers a poor prognosis for multiple myeloma patients. This has been known for many years and forms the basis of the Revised International Staging system (R-ISS),[1] along with the presence of a t(4;14) and/or t(14;16), and high serum lactate dehydrogenase (LDH), low serum albumin, and high serum β2-microglobulin. A number of recent publications, however, have shown that it is not quite as straightforward as it seems and, as with many things, the devil is in the detail.

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The percentage of myeloma cells with del(17p) by fluorescent in situ hybridization (FISH), or if performed by sequencing, the clonal cancer fraction (CCF), has a major impact on outcome. FISH tests are usually reported as positive or negative, depending on a predefined cut-point initially determined on normal cells and often set at 2-5%. The presence of tumor heterogeneity is now well-recognized and over the years, different collaborative groups have recommended different cut-points for the presence of del(17p), with clinical significance ranging from >20% to >60% of affected cells.

A recent study performed by Thakurta and colleagues[2] utilized data from 1273 newly diagnosed multiple myeloma cases and demonstrated that the survival of cases decreased as the percentage of cells with del(17p) increased. They segmented cases by the percentage of abnormal cells, using increments of 10% between 30% to 80% abnormal cells, and they found that the optimal threshold for predicting a very poor outcome was between

55% and 64%. This represents approximately 8% of myeloma cases. When outcomes were stratified by a 55% threshold, cases with lower values had significantly longer overall survival (OS) and progression-free survival (PFS) compared with those with higher values (median OS, 84.1 vs 36 months and median PFS, 23.9 vs 14.3 months, respectively).

The presence of *TP53* mutation (*TP53*mut) is also important. Walker and colleagues[3] reported that mutations occur in approximately 3% of newly diagnosed cases and cases with *TP53*mut have a significantly poorer PFS compared with wild type (wt) cases (median 13.7 vs 26.9 months, *P*<0.001). Thanendrarajan and colleagues[4] found a significant correlation between *TP53*mut and del(17p), with the odds of having *TP53*mut increasing by 1.3-fold when there was a 10% increase in the percentage of cells carrying del(17p) (*P*=0.04). Corre and colleagues[5] extended these findings and showed that the mutation was more frequent (approximately 30%) when cases had del(17p) in 60% of cells. Cases with del(17p) and *TP53*mut, i.e., biallelic inactivation of *TP53*, had a particularly poor outcome.

Given the co-occurrence of del(17p) and *TP53*mut, there is some debate about whether the poor outcome is due to the actual percentage of cells with the deletion or the presence of the mutation. In the largest series reported to date (no del[17p], n = 2505; del[17p]/TP53wt, n = 76; and del[17p]/*TP53*mut, n = 45),[5] the cases with the worse outcome were those with del(17p)/*TP53*mut (median OS, 36.0 months; median PFS 18.1 months), whereas cases with del(17p)/*TP53*wt had an intermediate outcome (median OS, 52.8 months; median PFS, 27.2 months) compared with the best outcome in those without either abnormality (median OS 152.2 months; median PFS, 44.2 months).[5]

It is important to remember that other copy number abnormalities within the myeloma genome interact with del(17p) and contribute to prognosis. For example, Boyd and colleagues[6] demonstrated that the presence of adverse chromosome translocations [t(4;14), t(14;16), t(14;20)] and 1q gain or amplification increased risk. They defined a favorable risk group by the absence of adverse genetic lesions, an intermediate group as one with one adverse lesion, and a high-risk group by the co-segregation of more than one adverse lesion. More recently, Walker and colleagues[7] described a group of cases, referred to as "double-hit," with a particularly poor prognosis. This high-risk subgroup was defined by either a) bi-allelic *TP53* inactivation or b) amplification (≥4 copies) of 1q21 on the background of ISS Stage III, and comprised 6% of the population (median PFS, 15.4 months; median OS, 20.7 months).[3]

> "A combination of del(17p) and mutation can define a group of patients with a dire prognosis despite modern therapies that should be considered for novel therapeutic approaches."

Thanendrarajan and colleagues[4] also looked at the role of 17p in the context of high-risk defined by gene expression profiling (GEP)-70. They noted that the presence of del(17p) in more than 20% of cells was identified more than twice as frequently in GEP-70 high-risk patients compared with low-risk patients (21% vs 8%). In addition, the cut-point for clinical significance differed between the GEP-70 high- and low-risk groups. Consistent with the data from Thakurta[2] and Corre,[5] in the low-risk group a cut-point of 60% was associated with significantly impaired outcome compared with cases with a lower percentage of del(17p) positive cells (3-year OS, 73% vs 87%, *P*=0.002; 3-year PFS, 64% vs 81%, *P*=0.004). In the GEP high-risk cases, the prognostic importance of the cut-point was not seen, as high-risk cases with del(17p) in more than 20% of cells had a worse clinical outcome than cases without del(17p) (3-year OS, 62% vs 26%, *P*=0.007; 3-year PFS, 45% vs 17%, *P*=0.07), and this was consistent across all cut-points.

In conclusion, prior to assigning risk in multiple myeloma, it is essential to look for the presence of del(17p), and to quantify the number of cells carrying the abnormality, and to take into account bi-allelic inactivation (through homozygous deletion or concurrent mutation), and GEP-defined risk status, if possible. Importantly, cases with 17p abnormalities in less than 60% cells may not actually be clinically high-risk and other factors need to be considered. On the other hand, a combination of del(17p) and mutation can define a group of patients with a dire prognosis despite modern therapies that should be considered for novel therapeutic approaches.

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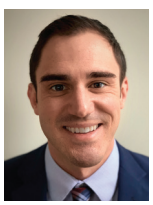
UNDERSTANDING THE PATIENT'S EXPERIENCE IN MYELOMA CARE – A CONVERSATION BETWEEN MYELOMA PATIENTS AND A MYELOMA SPECIALIST

The Leukemia & Lymphoma Society

Communication between the clinician and patient as a two-way conversation, clarity on goals for treatment and treatment protocol, patient education, and support from other members of the healthcare team, can all contribute to adherence to therapy and overall quality of life.

To better understand the patient experience, our Editor-in-Chief, Dr. Saad Usmani, and The Leukemia & Lymphoma Society had a Virtual Roundtable discussion with Ethan and Yelak, two myeloma survivors, to learn more about each of their cancer journeys from diagnosis as a young adult, underscoring the importance of communication and connection with other patients.

Dr. Usmani: Ethan and Yelak, please share your myeloma story. Tell us about the experiences that helped you along your journey and what experiences you felt could have been better. I would also like to hear about getting the information you specifically needed, seeking expert information. We know there is a lot of misinformation out there, as well as accurate information.



Ethan is a 30-year-old diagnosed with multiple myeloma in July 2013. He is doing excellent now and has become an experienced patient advocate by helping others affected by cancer, with an emphasis on multiple myeloma.

Ethan: I was diagnosed with myeloma at age 22, summer of 2013. Involvement in the myeloma community has helped me the most. This includes advocacy work, working closely with physicians, and trying to understand and expose myself to as much of the clinical information about multiple myeloma as possible. So much of it can go over your head so quickly. For example, the CRAB criteria. I presented with two bone lesions, and not much of it made sense to me at the time, as I was hearing so much about blood counts and other information. I focused on the bone lesions specifically. **Now, eight years later, I am starting to understand all the multiple myeloma criteria.**

I appreciate the work that has gone into the newer treatment landscape and that there are so many options available now. It is so exciting for patients, but it can also create confusion when a patient hears about a treatment that works well for one person, and wonders why it is not offered to them. So much can be categorized into the type of agent and their own staging, first or second relapse. I love learning about smoldering criteria, first degree relatives that may be at higher risk for MGUS, those of African American descent, trying to learn about how myeloma can possibly be intercepted earlier, how that treatment paradigm works as well, and CAR T therapies.

I like learning about and meeting other young cancer patients with shared experiences. Forming these bonds has created a sense of community in what otherwise can be a very isolating disease. At diagnosis, there was so much information provided, it was overwhelming. **Looking back, hearing less detailed information right at diagnosis**

along with the options for a treatment plan, would have been more helpful. Becoming more knowledgeable about pre-conditions, **including smoldering myeloma and MGUS, and the CRAB criteria has helped me better understand my journey along the way.**

Dr. Usmani: Thank you. I really like the way you outlined your journey with myeloma and what excites you. And now I am excited for you to hear Yelak's description, fast forwarding your journey by about 15 to 18 years.

Yelak is a patient turned Myeloma research advocate and has been able to successfully integrate Myeloma into his life for over a quarter of a century. Diagnosed at a young age of 25 with stage III Myeloma in 1995, Yelak is a member of the International Myeloma Foundation board of directors, ECOG's patient advocate and myeloma committees, NCI's Myeloma Steering Committee (MYSC), the NCI Council of Research Advocates (NCRA), and various pharma patient leadership councils, and is active on Twitter under the handle @NorthTxMsg.

Yelak: I was diagnosed young too, at age 25, in 1995. I thought I held the record of being young, but then I met Ethan. When I was diagnosed, there was no novel therapy. What was available was high-dose chemotherapy, followed by another high-dose chemotherapy, and then transplant. I also had bone involvement, it was not one or two. I had head-to-toe lesions all over my body, and significant involvement in the plasma cells and high M-spike. The good thing is I responded to what may now be considered salvage treatment.

For me, being able to see the evolution of treatments and outcomes was important. I think you can almost see the survival curves jump once the novel therapies came, and hopefully now, with antibody therapies, we will see another significant jump in overall survival for patients with myeloma.

And, while it was difficult to have myeloma at a young age and early in the myeloma journey, it was also easy, because we had only had one or two treatments and we knew what to do. **Now, with the cocktail of available treatments, it is important to have a consultation with a myeloma specialist.**

I was introduced to a myeloma support group through LLS' First Connection peer support program (www.LLS.org/peer-peer-support). Then I became a member of a support group which allowed me to continue to learn about myeloma, connect with other patients, become an advocate for myself and, over time, also start advocating for others.

Another important benefit offered by LLS is the Co-Pay Assistance Program (www.LLS.org/copay) **for patients that can't afford the treatments they need.**

Ethan: Yes, I have seen the LLS Co-Pay Assistance Program mentioned on patient (social media) boards, so there is awareness about it. The financial toxicity that can happen is top of mind for so many patients and this is a helpful and great resource.

> "So many (treatment) options available now. It is so exciting for patients, but it can also create confusion when a patient hears about a treatment that works well for one person, and wonders why it is not offered to them."

Several years ago, I was introduced to LLS through a patient advocacy group. I participated in a panel discussion at a young adult (YA) cancer conference. It was exciting to meet other YA cancer patients and, ongoing, to connect and to bond with other myeloma patients, especially YAs, as the journey can be very lonely. Also, there are so many complexities to myeloma, that local and national resources available from LLS (www.LLS.org/support) and other organizations (www.LLS.org/resourcedirectory) can be very helpful.

Highlights from the LLS Podcast

TREATING THE NEWLY DIAGNOSED PATIENT

For the October 2021 *Treating Blood Cancers* **healthcare professional podcast episode,** Dr. Ken Miller sat down with Dr. Joshua Richter to discuss the physician's role in treating newly diagnosed patients. Here are some highlights.

Ken Miller, MD

Joshua Richter, MD

Dr. Miller: I've wondered as a community hematologist and oncologist when to start treatment. There are patients who have smoldering myeloma and it's a decision on what to do and when. How do you think through that situation?

Dr. Richter: This is a hot topic and a lot has to do with our definitions of what is truly a smoldering patient who is okay to watch and observe without directed therapy, and who needs therapy. For years we separated out things succinctly between smoldering myeloma, defined at more than 10% or more bad plasma cells or myeloma cells in the marrow, or greater than an M spike in the blood of 3 grams per deciliter but no CRAB symptoms, the classic CRAB they talk about: high calcium, renal problems, anemia, or bone lesions. And then myeloma patients, people who needed therapy were patients who had CRAB symptoms.

One of the biggest shifts in recent years was a major paper published, led by the group at the Mayo Clinic and Dr. S. Vincent Rajkumar, November 2014, Lancet Hematology. They looked at thousands of patients who had smoldering myeloma and tried to pick out independent risk factors for reasons that would make them progress, because we classically would say smoldering myeloma has a 10% chance per year of progression. But we know it's heterogeneous. In that group, there's some people who are 2% and some 80%. They found three things that if a smoldering patient had any of these three, they were about 80-90% likely to progress within the next two years. Now we consider treating those patients earlier on. We call those the SLiM criteria. CRAB has evolved. It's lost weight and is now the SLiM CRAB, S Stands for 60. If you have 60% or more plasma cells in your marrow, even if you don't have any CRAB symptoms, we consider treating you.

LI stands for light chain ratio. We measure the kappa and lambda levels in the blood and if your ratio of kappa to lambda or lambda to kappa is greater than 100 to 1, you're at such a high risk of progression, we consider treating you.

M stands for MRI. In the old days the B for bone lesions came from old classic x-rays. We know patients can have lesions on MRI or PET CT years before it shows up on plain film. So, the definition is now if you have more than one lesion of at least 5 millimeters on an MRI, we consider treating you.

Dr. Miller: I'd love to hear more about what MRI means in that setting?

Dr. Richter: That's one of the most important answers, the question is what does that really mean? The IMWG has kind of endorsed three modalities of imaging we call MRI, but we mean higher order imaging, or something better than an x-ray.

The old-fashioned skeletal survey or metastatic bone survey is no longer considered a standard of care. It doesn't get the high-resolution look at the bones, shows nothing about soft tissues, and some patients can have soft tissue plasma cytomas. The three recommended higher order modality imaging tests are either low dose whole body CT, PET CT, or whole-body MRI. For whole body we like to use at our institution, DWI, which is a special form of MRI called diffusion weighted MRI (or DW-MRI). This allows us to almost get that feel of a PET scan. What lesions are not only there, but are they active or not active?

Dr. Miller: If insurance authorizations were not an issue, do you have one you'd choose or one you'd recommend of those three?

Dr. Richter: In general, PET CT is probably my favorite because it gives a lot of great information, but there are a few advantages of the MRI. It's not radiation. If you're doing a lot of them, especially for young patients, you anticipate living a long time, you avoid radiation. The other benefit of the MRI is that many of our patients have back problems from non-myeloma reasons, and it helps delineate when someone says my back hurts, what's a disc out of place, what's a little arthritis, and what's really myeloma?

Dr. Miller: How has COVID affected your practice?

Dr. Richter: One of the biggest things has been TeleMedicine. If you live in a place where you don't have easy access to a myeloma center, you can visit any center, any myeloma physician, by TeleMedicine to help guide care. One of the biggest issues now is vaccination and booster vaccination and combined with therapy.

Listen to more of this conversation, including examples of what goes into treatment decisions and what's exciting, coming on the horizon, such as bispecific antibodies, at www.LLS.org/HCPpodcast.

Joshua Richter, MD, Assistant Professor, Myeloma Division, TISH Cancer Institute, Icahn School of Medicine, Mt. Sinai, New York.

Ken Miller, MD, medical oncologist and hematologist affiliated with University of Maryland Midtown Medical Center and Sinai Hospital of Baltimore; LLS volunteer, Maryland.

WE'RE HERE TO HELP YOUR PATIENTS.

A blood cancer diagnosis can be overwhelming to your patients. Blood cancer patients, including those with myeloma, can find hope, education, guidance and support from The Leukemia & Lymphoma Society (LLS).

Our Information Specialists complement the care you provide with FREE, in-depth personalized services that connect myeloma patients to specific financial assistance, patient education (including booklets, podcasts and webinars), online and in-person support, and the LLS Clinical Trial Support Center for assistance with clinical trials.

Patients and families can contact us at **800.955.4572** or go to **www.LLS.org/Myeloma**.

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