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Evolution in the Treatment of Newly Diagnosed, Transplant-Ineligible Patients With Multiple Myeloma

Announcer
Welcome to ReachMD. This Medical Industry feature, titled “Evolution in the Treatment of Newly Diagnosed Patients with Multiple Myeloma” is brought to you by Janssen Pharmaceuticals. The following program is intended for US healthcare professionals only and is not certified for continuing medical education.

Your host today is Dr. Charles Turck, and our guests are Dr. Shebli Atrash, Levine Cancer Institute, and Dr. Ruemu Birhiray, Hematology Oncology of Indiana in Indianapolis, who are paid consultants for Janssen and must present information in accordance with FDA guidelines. Please see the full Prescribing Information available on the Reach MD host page and at darzalexhcp.com.

Here’s your host, Dr. Charles Turck.

Dr. Turck
Multiple myeloma is a rare, incurable form of blood cancer. And it was estimated that 35,000 patients in the United States were diagnosed with multiple myeloma in 2021. This is ReachMD, and I’m Dr. Charles Turck. Joining me to explore treatment strategies for patients who are newly diagnosed are Dr. Shebli Atrash and Dr. Ruemu Birhiray. Dr. Atrash is a Clinical Assistant Professor of Medicine and a Hematological Medical Oncologist at the Atrium Health Levine Cancer Institute in Charlotte, North Carolina. Dr. Atrash, thanks for joining us.

Dr. Atrash
Thank you for having me.

Dr. Turck
And Dr. Birhiray is a Clinical Professor of Medicine at Marian University Medical School, and a Medical Oncologist at Hematology Oncology of Indiana in Indianapolis, Dr. Birhiray, thanks for being here today.

Dr. Birhiray
Thank you so much for having me.

Dr. Turck
Let's begin with an overview of the multiple myeloma treatment landscape. Dr. Atrash, how has the treatment landscape evolved in recent years? And what kind of impact has that had for newly diagnosed patients?

Dr. Atrash
Sure. Over the last decade, treatment options for patients with multiple myeloma have significantly expanded, which has improved outcomes for many patients, specifically those who are newly diagnosed. One of the biggest advancements in the treatment of newly diagnosed patients has been the introduction of autologous stem cell transplantation. But beyond that development, induction therapy options have also evolved significantly. We now have targeted tools, which offer different approaches to treating this disease. And we found that maintenance therapy following autologous stem cell transplant actually improves progression-free survival, or PFS. As a result of these and other treatment advances, the five-year survival rate for those patients have increased from about 25% to about 50% in the last decades, but we still need more options for treatment in multiple myeloma.

Dr. Turck

Now, Dr. Atrash, given the relapsing nature of multiple myeloma, what should we be thinking about when choosing a frontline treatment regimen?

Dr. Atrash
Sure, so to me, the approach we should be taking to treat newly diagnosed multiple myeloma patients is very straightforward. I think we should be starting with regimens that are proven to induce deep and durable responses, and can increase progression-free survival, and in some cases, might increase overall survival. The reason is that in a retrospective analysis, spearheaded by Dr. Rafael Fonseca of three databases, the OPTUM Commercial Claims database, the Optum Electronic Medical Record database, and the Surveillance, Epidemiology, and End Results Medicare Linked database. The data showed that for each line of therapy, the proportion of patients who receive a second line of therapy decreases by 50%. Attrition from patients with multiple myeloma leads to fewer opportunities to use an effective treatment over time, with treatment duration declining with each line of subsequent therapy. With all of that being said, I would consider changing my practice to incorporate new regimens in current clinical trials based on clinical data if it means my patient can benefit from certain regimen today. Perhaps I am open to the earlier evolution of new regimens because I focus solely on treating multiple myeloma patients and by nature, being an academic setting, I'm involved in clinical trials in my institution.

Dr. Turck
Moving to you, Dr. Birhiray, can you share some of the most recent advancements in treatment and speak to how they have shaped your therapeutic approach in the community setting?

Dr. Birhiray
So until 15 years ago, multiple myeloma, in my opinion, was a disease that just didn't have adequate therapies. For years, there's just been one standard of care for frontline treatment. But since I started practicing more than 20 years ago, we've seen significant improvements in treatment options. Now we have triplets, and quadruplets combinations. Today, the literature highlights increasing rates of remission, stringent complete responses, and complete responses. But there's still a small number of patients who don't respond to treatment.

The majority of patients are treated in a community setting. So oncologists like me, are typically the first to make a diagnosis.

So as soon as one of my patients is diagnosed with multiple myeloma, my goal is to start them on treatment that I think can significantly benefit the patient. And to make that decision, I factor in the patient's individual profile, including their age, health history, individual risk profiles, and comorbidities. From there, I look to the treatment guidelines, which are constantly evolving based on latest evidence, and that includes more treatment for newly diagnosed patients than ever before.

Ultimately, the decision depends on the patient's treatment preferences. And then finally, it's important to provide them with information so that they feel comfortable and informed to make the best decision.

Dr. Turck
For those just tuning in, you're listening to ReachMD. I'm Dr. Charles Turck. And joining me to explore treatment advancements for patients with newly diagnosed multiple myeloma are Dr. Shebli Atrash and Dr. Ruemu Birhiray.

Announcer
Now that we've learned more about some of these treatment advancements let's focus on a specific treatment option for patients with newly diagnosed multiple myeloma, DARZALEX *FASPRO*®. But before we dive in, let's review the indications and some of the Important Safety Information for DARZALEX® (daratumumab), administered intravenously, and DARZALEX *FASPRO*® (daratumumab and hyaluronidase human-fihj), administered subcutaneously.

DARZALEX® (daratumumab) is indicated for the treatment of adult patients with multiple myeloma:

• In combination with lenalidomide and dexamethasone in newly diagnosed patients who are

ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple

myeloma who have received at least one prior therapy

• In combination with bortezomib, melphalan, and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant

• In combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed patients

who are eligible for autologous stem cell transplant

• In combination with bortezomib and dexamethasone in patients who have received at least one prior therapy

• In combination with carfilzomib and dexamethasone in patients with relapsed or refractory multiple myeloma who have received one to three prior lines of therapy

• In combination with pomalidomide and dexamethasone in patients who have received at least two prior therapies including lenalidomide and a proteasome inhibitor (PI)

• As monotherapy in patients who have received at least three prior lines of therapy including a PI and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent

DARZALEX *FASPRO*® (daratumumab and hyaluronidase-fihj) is indicated for the treatment of adult patients with multiple myeloma:

• In combination with bortezomib, melphalan, and prednisone in newly diagnosed patients who

are ineligible for autologous stem cell transplant

• In combination with lenalidomide and dexamethasone in newly diagnosed patients who are

ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple

myeloma who have received at least one prior therapy

• In combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed patients

who are eligible for autologous stem cell transplant

• In combination with pomalidomide and dexamethasone in patients who have received at least

one prior line of therapy including lenalidomide and a proteasome inhibitor (PI)

• in combination with carfilzomib and dexamethasone in patients with relapsed or refractory multiple myeloma who have received one to three prior lines of therapy

• In combination with bortezomib and dexamethasone in patients who have received at least one prior therapy

• As monotherapy in patients who have received at least three prior lines of therapy including a PI and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent

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DARZALEX *FASPRO*®is contraindicated in patients with a history of severe hypersensitivity to daratumumab, hyaluronidase or any of the components of the formulation.

DARZALEX® can cause severe and/or serious infusion-related reactions including anaphylactic reactions.

Both systemic administration-related reactions, including severe or life-threatening reactions, and local injection-site reactions can occur with DARZALEX *FASPRO*®. Fatal reactions have been reported with daratumumab-containing products, including DARZALEX *FASPRO*®. Additional Important Safety Information will be presented later during this presentation.

Dr. Turck

Dr. Birhiray, let's dive into DARZALEX *FASPRO*® as a treatment option for patients with newly diagnosed multiple myeloma. What can you tell us about the adoption of this new treatment option?

Dr. Birhiray

For a long time, I would actually start my patients on treatment with an appropriate DARZALEX® regimen due to its strong efficacy profile. Initially, the intravenous formulation was only approved in regimens for relapse or refractory patients. But over time, additional regimens were approved to include newly diagnosed patients. So when DARZALEX *FASPRO*® was approved, we were able to administer therapy that is expected to give the same efficacy as the I.V. formulation, but could be provided in a much shorter period of time, in a way that this very patient-friendly regimen frees up resources. The fixed dose provides additional flexibility for patients and for healthcare providers and practices.

While the exact dosing schedule of DARZALEX *FASPRO*® depends on the treatment regimen prescribed, over time, treatments are often needed every four weeks, giving a substantial amount of time back to both patients or healthcare providers. For me, this was a

compelling reason to switch. And it's a major advancement in the treatment of myeloma. Some of my longer-term patients who have been doing well with DARZALEX®, have had some hesitancy by changing anything from the administration option that had been working for them. I understand that, but that's why it's important for me to explain that the efficacy is the same as with the intravenous formulation. That said, of course, if patients are most comfortable staying on their current I.V. regimen, the decision is theirs.

Dr. Turck
Dr. Atrash, can you tell us a little bit about your experience with DARZALEX *FASPRO*®?

Dr. Atrash
Sure. I agree with a lot of what Dr. Birhiray has said. And to me those were very compelling reasons to adapt DARZALEX *FASPRO*® into my practice. In my experience, the side effects profile is acceptable, and the efficacy is comparable to I.V. infusion treatments. In the academic settings, we are also facing challenges with time in the infusion centers. With the reduced administration time for DARZALEX® *FASPRO*®, clinicians are able to accommodate a larger volume of patients, and patients spend less time receiving treatment.

Dr. Turck
Thanks for that insight. Dr. Atrash, as we look towards the future, are there any other clinical trials or research developments that might impact the treatment landscape for newly diagnosed patients?

Dr. Atrash
Thank you for this question. The treatment landscape is constantly evolving and has transformed significantly over the last five years. But there are many more advances on the horizon. For physicians who are treating newly diagnosed transplant ineligible patients, the use of DARZALEX® with lenalidomide and dexamethasone, DARZALEX® Rd regimen was explored in the phase 3 MAIA clinical trial.

Dr. Turck
It's a great way to round out our discussion on this topic. I'd like to thank Dr. Shebli Atrash and Dr. Ruemu Birhiray for sharing their insights on treating newly diagnosed multiple myeloma.

Dr. Atrash
Thank you for having us.

Dr. Birhiray
Thank you.

Dr. Turck
For our listeners, before we conclude, let's review some important safety information for DARZALEX® and DARZALEX *FASPRO*®.

Announcer
DARZALEX®and DARZALEX *FASPRO*® IMPORTANT SAFETY INFORMATION

DARZALEX® AND DARZALEX *FASPRO*®: CONTRAINDICATIONS

DARZALEX® and DARZALEX *FASPRO*® are contraindicated in patients with a history of severe hypersensitivity to daratumumab, hyaluronidase (for DARZALEX *FASPRO*®), or any of the components of the formulations.

DARZALEX® Infusion-Related Reactions

DARZALEX® can cause severe and/or serious infusion-related reactions including anaphylactic reactions. These reactions can be life-threatening, and fatal outcomes have been reported. In clinical trials (monotherapy and combination: N=2066), infusion-related reactions occurred in 37% of patients with the Week 1 (16 mg/kg) infusion, 2% with the Week 2 infusion, and cumulatively 6% with subsequent infusions. Less than 1% of patients had a Grade 3/4 infusion-related reaction at Week 2 or subsequent infusions. The median time to onset was 1.5 hours (range: 0 to 73 hours). Nearly all reactions occurred during infusion or within 4 hours of completing DARZALEX®. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnea, hypertension, tachycardia, headache, laryngeal edema, pulmonary edema, and ocular adverse reactions, including choroidal effusion, acute myopia, and acute angle closure glaucoma.

Signs and symptoms may include respiratory symptoms, such as nasal congestion, cough, throat irritation, as well as chills, vomiting, and nausea. Less common signs and symptoms were wheezing, allergic rhinitis, pyrexia, chest discomfort, pruritus, hypotension, and blurred vision.

When DARZALEX® dosing was interrupted in the setting of ASCT (CASSIOPEIA) for a median of 3.75 months (range: 2.4 to 6.9 months), upon re-initiation of DARZALEX®, the incidence of infusion-related reactions was 11% for the first infusion following ASCT. Infusion-related reactions occurring at re-initiation of DARZALEX® following ASCT were consistent in terms of symptoms and severity (Grade 3 or 4: <1%) with those reported in previous studies at Week 2 or subsequent infusions. In EQUULEUS, patients receiving combination treatment (n=97) were administered the first 16 mg/kg dose at Week 1 split over two days, ie, 8 mg/kg on Day 1 and Day 2, respectively. The incidence of any grade infusion-related reactions was 42%, with 36% of patients experiencing infusion-related reactions on Day 1 of Week 1, 4% on Day 2 of Week 1, and 8% with subsequent infusions.

Pre-medicate patients with antihistamines, antipyretics, and corticosteroids. Frequently monitor patients during the entire infusion. Interrupt DARZALEX® infusion for reactions of any severity and institute medical management as needed. Permanently discontinue DARZALEX® therapy if an anaphylactic reaction or life-threatening (Grade 4) reaction occurs and institute appropriate emergency care. For patients with Grade 1, 2, or 3 reactions, reduce the infusion rate when re-starting the infusion.

To reduce the risk of delayed infusion-related reactions, administer oral corticosteroids to all patients following DARZALEX® infusions. Patients with a history of chronic obstructive pulmonary disease may require additional post-infusion medications to manage respiratory complications. Consider prescribing short- and long-acting bronchodilators and inhaled corticosteroids for patients with chronic obstructive pulmonary disease.

Ocular adverse reactions, including acute myopia and narrowing of the anterior chamber angle due to ciliochoroidal effusions with potential for increased intraocular pressure or glaucoma, have occurred with DARZALEX® infusion. If ocular symptoms occur, interrupt DARZALEX® infusion and seek immediate ophthalmologic evaluation prior to restarting DARZALEX®.

DARZALEX *FASPRO*®: Hypersensitivity and Other Administration Reactions

Both systemic administration-related reactions, including severe or life-threatening reactions, and local injection-site reactions can occur with DARZALEX *FASPRO*®. Fatal reactions have been reported with daratumumab-containing products, including DARZALEX *FASPRO*®.

Systemic Reactions

In a pooled safety population of 898 patients with multiple myeloma (N=705) or light chain (AL) amyloidosis (N=193) who received DARZALEX *FASPRO*® as monotherapy or in combination, 9% of patients experienced a systemic administration-related reaction (Grade 2: 3.2%, Grade 3: 1%). Systemic administration-related reactions occurred in 8% of patients with the first injection, 0.3% with the second injection, and cumulatively 1% with subsequent injections. The median time to onset was 3.2 hours (range: 4 minutes to 3.5 days). Of the 140 systemic administration-related reactions that occurred in 77 patients, 121 (86%) occurred on the day of DARZALEX *FASPRO*® administration. Delayed systemic administration-related reactions have occurred in 1% of the patients.

Severe reactions included hypoxia, dyspnea, hypertension, tachycardia, and ocular adverse reactions, including choroidal effusion, acute myopia, and acute angle closure glaucoma. Other signs and symptoms of systemic administration-related reactions may include respiratory symptoms, such as bronchospasm, nasal congestion, cough, throat irritation, allergic rhinitis, and wheezing, as well as anaphylactic reaction, pyrexia, chest pain, pruritus, chills, vomiting, nausea, hypotension, and blurred vision.

Pre-medicate patients with histamine-1 receptor antagonist, acetaminophen, and corticosteroids. Monitor patients for systemic administration-related reactions, especially following the first and second injections. For anaphylactic reaction or life-threatening (Grade 4) administration-related reactions, immediately and permanently discontinue DARZALEX *FASPRO*®. Consider administering corticosteroids and other medications after the administration of DARZALEX *FASPRO*® depending on dosing regimen and medical history to minimize the risk of delayed (defined as occurring the day after administration) systemic administration-related reactions.

Ocular adverse reactions, including acute myopia and narrowing of the anterior chamber angle due to ciliochoroidal effusions with potential for increased intraocular pressure or glaucoma, have occurred with daratumumab-containing products. If ocular symptoms occur, interrupt DARZALEX *FASPRO*® and seek immediate ophthalmologic evaluation prior to restarting DARZALEX *FASPRO*®.

Local Reactions

In this pooled safety population, injection-site reactions occurred in 8% of patients, including Grade 2 reactions in 0.7%. The most frequent (>1%) injection-site reaction was injection-site erythema. These local reactions occurred a median of 5 minutes (range: 0 minutes to 6.5 days) after starting administration of DARZALEX *FASPRO*®. Monitor for local reactions and consider symptomatic management.

DARZALEX® and DARZALEX *FASPRO*®: Neutropenia and Thrombocytopenia

DARZALEX® and DARZALEX *FASPRO*® may increase neutropenia and thrombocytopenia induced by background therapy. Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. Consider withholding DARZALEX® or DARZALEX *FASPRO*® until recovery of neutrophils or for recovery of platelets.

In lower body weight patients receiving DARZALEX *FASPRO*®, higher rates of Grade 3-4 neutropenia were observed.

DARZALEX® and DARZALEX *FASPRO*®: Interference With Serological Testing

Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive indirect antiglobulin test (indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab administration. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum. The determination of a patient's ABO and Rh blood type are not impacted. Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received DARZALEX® and DARZALEX *FASPRO*®. Type and screen patients prior to starting DARZALEX® and DARZALEX *FASPRO*®.

DARZALEX® and DARZALEX *FASPRO*®: Interference With Determination of Complete Response

Daratumumab is a human immunoglobulin G (IgG) kappa monoclonal antibody that can be detected on both the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein. This interference can impact the determination of complete response and of disease progression in some patients with IgG kappa myeloma protein.

DARZALEX® and DARZALEX *FASPRO*®: Embryo-Fetal Toxicity

Based on the mechanism of action, DARZALEX® and DARZALEX *FASPRO*® can cause fetal harm when administered to a pregnant woman. DARZALEX® and DARZALEX *FASPRO*® may cause depletion of fetal immune cells and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use effective contraception during treatment with DARZALEX® or DARZALEX *FASPRO*® and for 3 months after the last dose.

The combination of DARZALEX® or DARZALEX *FASPRO*® with lenalidomide, pomalidomide, or thalidomide is contraindicated in pregnant women because lenalidomide, pomalidomide, and thalidomide may cause birth defects and death of the unborn child. Refer to the lenalidomide, pomalidomide, or thalidomide prescribing information on use during pregnancy.

DARZALEX®: ADVERSE REACTIONS

The most frequently reported adverse reactions (incidence ≥20%) were upper respiratory infection, neutropenia, infusion-related reactions, thrombocytopenia, diarrhea, constipation, anemia, peripheral sensory neuropathy, fatigue, peripheral edema, nausea, cough, pyrexia, dyspnea, and asthenia. The most common hematologic laboratory abnormalities (≥40%) with DARZALEX® are neutropenia, lymphopenia, thrombocytopenia, leukopenia, and anemia.

DARZALEX *FASPRO*®: ADVERSE REACTIONS

In multiple myeloma, the most common adverse reaction (≥20%) with DARZALEX *FASPRO*® monotherapy is upper respiratory tract infection. The most common adverse reactions with combination therapy (≥20% for any combination) include fatigue, nausea, diarrhea, dyspnea, insomnia, headache, pyrexia, cough, muscle spasms, back pain, vomiting, hypertension, upper respiratory tract infection, peripheral sensory neuropathy, constipation, pneumonia, and peripheral edema. The most common hematologic laboratory abnormalities (≥40%) with DARZALEX *FASPRO*® are decreased leukocytes, decreased lymphocytes, decreased neutrophils, decreased platelets, and decreased hemoglobin.

Announcer

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