cure® EDUCATED PATIENT®

MULTIPLE MYELOMA SUMMIT

Conference Report

VIRTUAL CONFERENCE | November 21, 2020

EXPERTS DISCUSS MYELOMA TREATMENT UPDATES

WHAT YOU NEED TO KNOW

- Evolving Treatment Standards for the Newly Diagnosed
- Improving Outcomes With Diagnosis and Staging
- New Treatments in the Relapsed/Refractory Setting
- Myeloma 101: Understanding the Disease
- Clinical Trials in Smoldering Myeloma
- And more!

Presented by

cure®

INDICATION AND IMPORTANT SAFETY INFORMATION FOR DARZALEX®

DARZALEX® (daratumumab) is a prescription medicine used to treat adult patients with multiple myeloma:

- In combination with the medicines lenalidomide and dexamethasone in people with newly diagnosed multiple myeloma who cannot receive a type of stem cell transplant that uses their own stem cells (autologous stem cell transplant) and in people who have received at least one prior medicine to treat multiple myeloma

It is not known if DARZALEX® is safe and effective in children.

IMPORTANT SAFETY INFORMATION FOR DARZALEX® (daratumumab)

Do not receive DARZALEX® if you have a history of a severe allergic reaction to daratumumab or any of the ingredients in DARZALEX®. See the ingredients for DARZALEX® below.

Before you receive DARZALEX®, tell your healthcare provider about all of your medical conditions, including if you:

- have a history of breathing problems
- have had shingles (herpes zoster)
- have ever had or might now have a hepatitis B infection as DARZALEX® could cause hepatitis B virus to become active again. Your healthcare provider will check you for signs of this infection before, during and for some time after treatment with DARZALEX®. Tell your healthcare provider right away if you get worsening tiredness or yellowing of your skin or white part of your eyes
- are pregnant or plan to become pregnant. DARZALEX® may harm your unborn baby
  - Females who are able to become pregnant should use an effective method of birth control during treatment and for at least 3 months after your final dose of DARZALEX®. Talk to your healthcare provider about birth control methods that you can use during this time
- are breastfeeding or plan to breastfeed. It is not known if DARZALEX® passes into your breast milk

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive DARZALEX®?

- DARZALEX® may be given alone or together with other medicines used to treat multiple myeloma
- DARZALEX® will be given to you by your healthcare provider by intravenous (IV) infusion into your vein
- Your healthcare provider will decide the time between doses as well as how many treatments you will receive
- Your healthcare provider will give you medicines before each dose of DARZALEX® and after each dose of DARZALEX® to help reduce the risk of infusion reactions
- If you miss any appointments, call your healthcare provider as soon as possible to reschedule your appointment

DARZALEX® may cause serious reactions, including:

- **Infusion reactions.** Infusion reactions are common with DARZALEX® and can be severe or serious. Your healthcare provider may temporarily stop your infusion or completely stop treatment with DARZALEX® if you have infusion reactions. Get medical help right away if you get any of the following symptoms: shortness of breath or trouble breathing, dizziness or lightheadedness (hypotension), cough, wheezing, throat tightness, runny or stuffy nose, headache, itching, nausea, vomiting, chills, or fever.
- **Changes in blood tests.** DARZALEX® can affect the results of blood tests to match your blood type. These changes can last for up to 6 months after your final dose of DARZALEX®. Your healthcare provider will do blood tests to match your blood type before you start treatment with DARZALEX®. **Tell all of your healthcare providers that you are being treated with DARZALEX® before receiving blood transfusions.**
- **Decreases in blood cell counts.** DARZALEX® can decrease white blood cell counts, which help fight infections, and blood cells called platelets, which help to clot blood. Your healthcare provider will check your blood cell counts during treatment with DARZALEX®. Tell your healthcare provider if you develop fever or have signs of bruising or bleeding.

The most common side effects of DARZALEX® include: tiredness; nausea; diarrhea; shortness of breath; trouble sleeping; feeling weak; decreased appetite; fever; cough; muscle spasms; back pain; joint pain; vomiting; bronchitis; cold-like symptoms (upper respiratory infection); nerve damage causing tingling, numbness or pain; swollen hands, ankles or feet; constipation; chills; dizziness; and lung infection (pneumonia).

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of DARZALEX®. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of DARZALEX®

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your healthcare provider or pharmacist for information about DARZALEX® that is written for health professionals.

What are the ingredients in DARZALEX®?

Active ingredient: daratumumab
Inactive ingredients: glacial acetic acid, mannitol, polysorbate 20, sodium acetate trihydrate, sodium chloride, and water for injection

cp-101876v3

Please see a Brief Summary of the Important Product Information on adjacent pages.

janssen

DARZALEX®
(daratumumab)
injection for intravenous infusion
100 mg/5 mL, 400 mg/20 mL

IT'S A NEW DAY

WITH DARZALEX® ON YOUR TEAM

For adults with newly diagnosed multiple myeloma who cannot receive a stem cell transplant

Ask your doctor about DARZALEX®

DARZALEX® may help you live longer without your multiple myeloma getting worse

DARZALEX® in combination with Revlimid® (lenalidomide) + dexamethasone (DRd) was proven effective in a clinical study of adults who were newly diagnosed with multiple myeloma and cannot receive a type of stem cell transplant that uses their own cells (autologous stem cell transplant).*

74% of patients treated with **DARZALEX® + Rd** (n=368) lived without their disease getting worse vs **61% of patients treated with Rd alone** (n=369).†

†At a **median** follow-up of 28 months.

*The main goals of the study were to measure the length of time patients lived without their multiple myeloma getting worse and how many people responded to treatment.

More patients responded to DARZALEX® in combination with Rd vs Rd alone

9 out of 10 patients

93% of patients responded to **DARZALEX® + Revlimid® + dexamethasone** vs **81% of patients treated with Rd alone**.

DARZALEX® is **not chemotherapy**. It is an **immunotherapy** that works with your immune system. DARZALEX® targets a specific protein on multiple myeloma cells and may also affect normal cells with this protein. DARZALEX® can cause serious side effects, including infusion reactions and decreases in blood cell counts. **See Important Safety Information on the facing page and Patient Information on the following page.**

PATIENT INFORMATION
DARZALEX® (Dar'-zah-lex)
(daratumumab)
injection, for intravenous use

What is DARZALEX?

DARZALEX is a prescription medicine used to treat adults with multiple myeloma:

- in combination with the medicines lenalidomide and dexamethasone in people with newly diagnosed multiple myeloma who cannot receive a type of stem cell transplant that uses their own stem cells (autologous stem cell transplant) and in people who have received at least one prior medicine to treat multiple myeloma.
- in combination with the medicines bortezomib, melphalan and prednisone, in people with newly diagnosed multiple myeloma who cannot receive a type of stem cell transplant that uses their own stem cells (autologous stem cell transplant).
- in combination with the medicines bortezomib, thalidomide, and dexamethasone in newly diagnosed people who are eligible to receive a type of stem cell transplant that uses their own stem cells (autologous stem cell transplant).
- in combination with the medicines bortezomib and dexamethasone, in people who have received at least one prior medicine to treat multiple myeloma.
- in combination with the medicines pomalidomide and dexamethasone in people who have received at least two prior medicines to treat multiple myeloma, including lenalidomide and a proteasome inhibitor.
- alone in people who have received at least three prior medicines, including a proteasome inhibitor and an immunomodulatory agent, **or** did not respond to a proteasome inhibitor and an immunomodulatory agent.

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Do not receive DARZALEX:

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- feeling weak
- decreased appetite
- fever
- cough
- muscle spasms
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- joint pain
- vomiting
- bronchitis
- cold-like symptoms (upper respiratory infection)
- nerve damage causing tingling, numbness or pain
- swollen hands ankles or feet
- constipation
- chills
- dizziness
- lung infection (pneumonia)

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Inactive ingredients: glacial acetic acid, mannitol, polysorbate 20, sodium acetate trihydrate, sodium chloride, and water for injection

Manufactured by: Janssen Biotech, Inc., Horsham, PA 19044 U.S. License Number 1864
For more information, call 1-800-526-7736 or go to www.DARZALEX.com.

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More Options and Varying Opinions Mark the Treatment of Newly Diagnosed Multiple Myeloma

Evolving standards of care have given patients a wider variety of treatments, but they can also be disconcerting. Dr. Clifton Mo explores the treatment landscape and breaks down the details of the different drugs. By Jessica Skarzynski

OVER THE PAST DECADE or so, the wealth of treatment options in newly diagnosed multiple myeloma has given patients a wider variety of possibilities. Coupled with rapidly evolving standards of care, this can lead to confusion. But according to **Dr. Clifton Mo**, director of autologous stem cell transplantation for multiple myeloma at Dana-Farber Cancer Institute, these evolving standards only mean the treatments are improving.

DR. CLIFTON MO

"As anyone who's sought second or third opinions between different multiple myeloma centers can probably attest, you don't always walk out of the center with the same recommendation as the one before," Mo said. "And what I tell my patients is, I understand that that can be somewhat disconcerting."

At *CURE*®'s Educated Patient® Multiple Myeloma Summit, Mo spoke about how the treatment landscape of newly diagnosed multiple myeloma has evolved, from single-agent chemotherapy to highly effective combinations that are continually being examined and fine-tuned to offer patients the best outcomes.

As Mo explained, in the mid-1990s, the standard of care for this patient population was high-dose melphalan chemotherapy with autologous stem cell transplant. This plan was based on the results of two large studies that found a significant increase in overall survival in patients who were able to proceed to transplant with early high-dose melphalan compared with those who received only standard chemotherapy.

Then, after the development and approval of novel agent Velcade (bortezomib) in 2003, a new era of combined novel agent treatment began, with the most notable pair being the duo of Velcade and Revlimid (lenalidomide). "It was found that the combination of Revlimid with the proteasome inhibitor Velcade was very synergistic and was much more efficacious than single-agent novel therapy alone," Mo explained.

This combination led to further study, such as the 2012 landmark SWOG S0777 study comparing RVd (Revlimid, Velcade and dexamethasone) with single-agent Revlimid in patients without an immediate need for stem cell transplant. In this study, patients treated with the triplet-induction regimen saw a 29% survival advantage compared with the single-agent group, leading to a new standard of care in multiple myeloma and, as Mo explained, setting the stage for the current era of treatment.

But the introduction of Kyprolis (carfilzomib), a second-generation proteasome inhibitor similar to Velcade, set the stage for one of the first "great debates" in the treatment of newly diagnosed myeloma, Mo said.

First approved in the relapsed/refractory setting, Kyprolis was found to be a potent and promising drug. But researchers were then compelled to determine which was better: RVd or KRd (Kyprolis, Revlimid and dexamethasone).

"This is arguably one of the biggest debates within the multiple myeloma community," Mo noted. Although RVd demonstrated a 29% reduction in all-cause mortality compared with Revlimid alone in the SWOG S0777 study, researchers saw an impressive benefit of KRd compared with Revlimid alone in the relapsed/refractory setting thanks to the ASPIRE trial. Encouraging progression-free survival (the time from treatment to disease progression) rates were also seen in high-risk patients treated with KRd.

However, each treatment comes with its own side effects that need to be considered. "What we've known for a long time is that these two drugs have significant differences in terms of their toxicities and risks," Mo said. With Velcade, peripheral neuropathy is common though rarely dangerous. However, Kyprolis was shown to cause cardiotoxicity in less than 10% of patients, which, although uncommon, is also potentially very dangerous.

The debate about these two treatments continued mostly because there were no head-to-head data comparing them in the newly diagnosed setting until several months ago, when results of the phase 3 ENDURANCE (E1A11) trial were presented. And although the fiindings showed that KRd was not more effective than Revlimid — which remains the standard of care in this population — some critics noted that RVd is not a better choice than KRd, especially given the toxicities associated with each, and that the trial design was flawed.

Mo, however, believes that both are still solid options. "I'm going to hedge and say that they are still both within the realm

> **"In my opinion, the educated patient may actually know best."** —DR. CLIFTON MO

of standard of care, and both acceptable induction regimens for newly diagnosed patients who are transplant eligible. (Because) it's myeloma. So of course, it's not straightforward," he said.

"In my opinion, the educated patient may actually know best," Mo continued. "(Be) aware of data, (be) aware of the very real differences between toxicities and risks."

Another continuing debate in the treatment of newly diagnosed myeloma involves when to perform autologous stem cell transplant. With studies evaluating early versus delayed transplant, Mo uses a military analogy to explain the issue: "I look at this debate as a choice between essentially using the big guns up front versus low-intensity warfare."

Lastly, Mo examined the debates about the safety and efficacy of triplet therapy versus quad-induction therapy, which combines one of the standard triplets with a CD38 antibody, usually Darzalex (daratumumab). "On the one hand, we have triplets, and we know that they are highly efficacious. They're essentially overall very well tolerated. They're lower risk than the quads in terms of risk of infection and other toxicities, they have a proven survival advantage and — again, the elephant in the room — they are less expensive," Mo said. With a depth of response of less than 50%, quads have been found to have "unprecedented depths of response," albeit with a potentially greater risk of toxicity.

Ultimately, Mo noted, these debates and others in the myeloma community continue, with more trials looking at the pros and cons of every variety of combination, all with the goal of providing patients with the safest and most effective treatments. ■

Accurate Diagnosis and Staging Improve Outcomes in Multiple Myeloma

Advancements in the diagnosis and staging of the disease continue to shape treatment decisions and boost results. *By Brielle Benyon*

THERE ARE MULTIPLE FACTORS that doctors take into consideration when diagnosing and staging multiple myeloma, leading to better treatment for the disease, **Dr. Nikhil C. Munshi** explained.

Munshi, director of basic and correlative science at the Jerome Lipper Multiple Myeloma Center at Dana-Farber Cancer Institute, recently discussed diagnosis and risk assessment in myeloma at *CURE*®'s Educated Patient® Multiple Myeloma Summit.

DR. NIKHIL C. MUNSHI

Diagnosis Requires Blood Test

To diagnose myeloma, doctors traditionally start with a blood test. Then, they usually conduct a bone marrow biopsy to determine how many myeloma cells are in the patient's bone marrow. Finally, patients may undergo an X-ray to see if there are any holes in the bones, which would indicate progressive disease.

"This is the standard work-up that we have been doing for the last 15 or more years," Munshi said. "But now, (clinicians) are doing many more things."

More recently, serum free light chain testing has become standard. These tests look at immunoglobulins, which are partially made up of light chains, in the blood. When there are more light chains than heavy chains, the immunoglobulin cannot bind to them, making them free in the blood. A high level of free light chains indicates that there may be a problem.

The blood tests used in myeloma diagnosis have evolved, too. Clinicians will perform protein electrophoresis to look for monoclonal spike, commonly referred to as "M spike." In doing so, they are able to test the amount of myeloma in the blood.

"A higher level means that there is more myeloma," Munshi explained. "When the level goes down, we know that the myeloma is being controlled."

This test can tell whether myeloma treatment is working. Now that there is a simple blood test, patients may not need to undergo bone marrow biopsies as much.

Prognosis Guides Treatment Decisions

Once myeloma is diagnosed, clinicians look at both the prognosis and the molecular makeup to determine the best treatment.

A patient with symptomatic myeloma — affected kidney function and/or bone lesions — should be treated.

X-rays and PET and CT scans are also used to determine to what extent the myeloma has affected the patient's bones and surrounding regions, such as the liver.

"In the old days, when bone marrow was involved 70%, 80% or even 90%, we wouldn't start treatment," Munshi said. "Now these new criteria tell us that if it is more than 60%, we should begin to think about treating this patient."

When it comes to prognosis, doctors analyze proteins such as albumin and beta 2 macroglobulin, as well as results from a fluorescence in situ hybridization genetic test.

"In looking at the genetic makeup of the multiple myeloma, we can establish the long-term plan. We could say, 'Since your myeloma is on the more aggressive side, we'll need to do treatment for a longer period of time,'" Munshi said.

However, he added, patients should not get caught up in their stage of myeloma. A late-stage (3 or 4) diagnosis might not be as deadly in myeloma as it is in other cancers. "The reason is that even those who are stage 3 do quite well with new treatment and with the new drugs we have," Munshi said, explaining that a patient might receive a multidrug maintenance regimen instead of a single-drug therapy.

"What we are beginning to do is incorporate more knowledge that we are gathering over time, looking at mutations and other things to make this next generation of staging a system that is comprehensive. And we need to keep that in mind," Munshi said. ■

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New Treatment Options Enter the Relapsed/Refractory Setting

The complexity of multiple myeloma can make it difficult to treat, but with that complexity comes more avenues for researchers to explore what treatments work best. By Conor Killmurray

DR. PAUL G. RICHARDSON

TREATMENT OPTIONS FOR multiple myeloma have significantly expanded in recent years, and that includes patients in the relapsed/refractory setting who often face an even more complex disease.

Patients with relapsed/refractory multiple myeloma have double the mutations of patients with newly diagnosed multiple myeloma, according to **Dr. Paul G. Richardson**, clinical program leader and director of clinical research at the Jerome Lipper Multiple Myeloma Center at Dana-Farber Cancer Institute in Boston. This complex disease has prompted investigators to examine a wide range of treatments, with multiple therapies approved by the Food and Drug Administration (FDA) and more being studied in clinical trials. More specifically, researchers are working to target mutations through lower-dose combination treatments that help reduce side effects, explained Richardson at *CURE*®'s Educated Patient® Multiple Myeloma Summit.

To learn more, *CURE*® spoke with Richardson about current and future treatment options for patients with relapsed/refractory multiple myeloma.

CURE®: In your panel presentation, you mentioned that multiple myeloma is complex. What makes it complex, and what's different for patients when they have relapsed/refractory disease?

Richardson: Multiple myeloma is an incredibly complex illness, both in its manifestations and in the pathobiology that underlines it. Its genetics are highly complex at diagnosis and relapse due to the mutational thrust that's inherent to the disease (and to) some of the therapies we might use. Genomic events can multiply. And then they can also be an entity called clonal evolution. At diagnosis, there are 5,000 mutations in a given patient's multiple myeloma, but at relapse — after stem

cell transplantation, induction therapy and maintenance — this patient's whole genome sequencing reveals over 12,000 mutations. So that is a reflection of some of the complexity of the pathobiology, which means that relapse/refractory strategies have to be (biologically derived and targeted), but ... a specific, genetically targeted approach is extremely challenging in the setting of so many mutations.

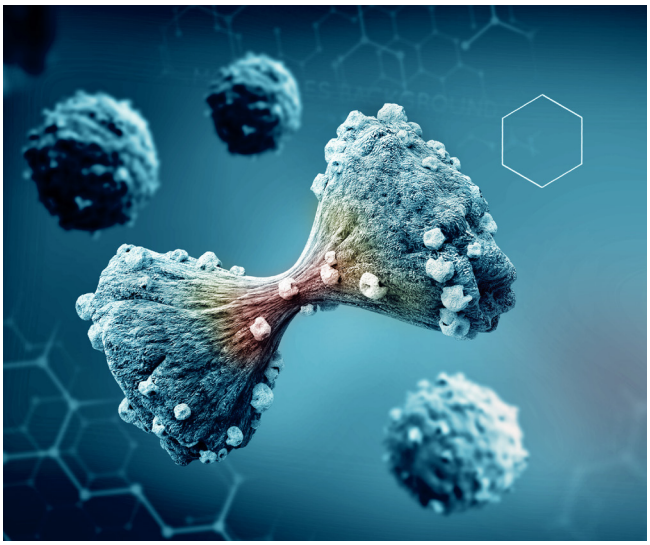
Are the many mutations the reason combination treatments are promising?

Combination strategies are absolutely essential. Currently, we have 12 approved drugs, (but) how do we sequence them? How do we combine them to throw a big net around this disease and shut it down? That becomes extremely important.

The options summarized in the presentation (included) proteasome inhibitors, immunomodulatory drugs and antibody targeting approaches. The targeting approaches with antibodies are very interesting because they incorporate Darzalex (daratumumab) and now most recently Sarclisa (isatuximab). And the data that support this (come from the) ICARIA-MM trial, with Pomalyst (pomalidomide) and dexamethasone (plus) Sarclisa in one arm of the study and pomalidomide and dexamethasone as the standard of care in the control group. We were able to show remarkable activity through this combination approach. The important point about Sarclisa is that it obviously targets CD38 (a glycoprotein that's highly expressed on multiple myeloma cells), but it also has a unique epitope that actually sets it apart from daratumumab. And it targets an actual enzyme uniformly expressed on myeloma cells through the CD38 mechanism. But importantly, it has more of an aphotic effect, as well as this inhibition of CD38 enzymic activity. So in addition to the immunological mechanisms, there are these direct effects that are qualitatively stronger with Sarclisa preclinically.

Now in terms of clinical activity, what we see is that when you can bear Sarclisa, there is almost a doubling of progression-free survival (the time from treatment to disease progression). We also see this whether patients have had two or three prior lines of therapy.

Very importantly, there's also a trend in survivorship pointing clearly to the ... three drugs versus the two and reflecting how Sarclisa is tolerated. There is no significant change in global quality of life or global health scale as a quality-of-life measure over time. So as a result of this, (Sarclisa) was FDA approved. Very importantly going forward, there are now very exciting data around the use of Sarclisa and Kyprolis (carfilzomib), which show similarly striking benefit in favor of Sarclisa, carfilzomib and dexamethasone.



Giovanni Cancemi / stock.adobe.com

In the relapsed/refractory setting, are treatment-related side effects worse? And are combination treatments reducing some of the side effects?

The good news is that combination approaches can allow the side effect profile to be much more manipulated and handled without losing efficacy. So, in other words, if you use three or four drugs together, you can have lower doses of each to achieve much more. Even so, sometimes it's appropriate to deploy a single agent or a doublet to try to really bring disease under control if a particular platform has failed a patient. I guess the short answer is that it very much depends. I would say that generally speaking, tolerability tends to be best earlier in the disease for a variety of reasons, because responses are quick and patients have not had to experience (as much therapy as) treatment-exposed relapsed/refractory patients. Because of that, the treatment-exposed relapsed/refractory patients can be more vulnerable to the side effects.

> **"Sometimes, from a symptomatic point of view, being forewarned is forearmed."**
>
> ***—DR. PAUL G. RICHARDSON***

So that's why sometimes in the relapsed/refractory setting, these side effects can appear magnified. Still, patients are experienced, and they know what they're feeling and they know why. Sometimes, from a symptomatic point of view, being forewarned is forearmed, and therefore, you're much more experienced at managing side effects. It's a very dynamic situation in terms of tolerability. In other words, some aspects of tolerability in early disease are more challenging than in later disease, but conversely, because a patient with relapsed/refractory disease has been more heavily pre-treated, certain side effects may be more challenging. ■

A Beginner's Guide to Understanding Myeloma

In an interview with CURE®, Dr. Giada Bianchi of the Dana-Farber Cancer Institute provides patients with an overview of myeloma, including symptoms and risk factors of the disease.

By Ryan McDonald

THE PAST 15 YEARS have proved pivotal for patients with myeloma, as the Food and Drug Administration (FDA) approved many active and highly specific therapies to treat the disease, according to **Dr. Giada Bianchi**.

Bianchi, an associate director of the Amyloidosis Program at Brigham and Women's Hospital and Dana-Farber Cancer Institute in Boston, recently provided an overview of myeloma during *CURE*®'s Educated Patient® Multiple Myeloma Summit.

In an interview with *CURE*®, Bianchi discussed what therapies are available to treat the disease and how patients can work with physicians to select the best therapy.

DR. GIADA BIANCHI

CURE®: How do you explain to patients what myeloma is and how it usually develops?

Bianchi: I'm a big fan of using drawings. When I meet with my patients, I do a very rudimentary drawing of what a plasma cell is and I explain how a normal plasma cell helps us by producing antibodies and fighting infection on our behalf.

From there, I talk about the fact that myeloma is a cancer of plasma cells that retain much of the capacity of normal plasma cells [while secreting] an abnormal protein or an abnormal immunoglobulin in the blood. That's often how we detect the disease and provide a diagnosis. And then I tell them that these cells typically live in the bone marrow, and when myeloma develops, rather than being a handful of cells in the bone marrow, [the cells] really start to grow disproportionately and impair the normal element of the bone marrow. The good cells of the blood, the platelets, the white cells and the red cells [affect] the integrity of the bone. Typically, patients present with bone pain related to bone disease from the exuberant growth of myeloma cells. Occasionally, the proteins that myeloma cells produce also can hurt the kidneys. Renal failure is another manifestation of this disease; together with a high calcium level, it often leads to the diagnosis.

You mention bone pain, but what are other symptoms?

The initial symptoms of myeloma may be very subtle, [such as] fatigue or a lack of stamina. This is often related to a degree of anemia or low hemoglobin in the blood that leads to the sensation of lack of energy. As far as pain, myeloma generally develops in the seventh decade of a patient's life, so it's not uncommon to have chronic back pain or bone pain related to degenerative joint disease. But any pain that is severe in nature, different in quality from what it was before or unremitting with normal conservative measures (should be noted). A patient with a history of MGUS (monoclonal gammopathy of undetermined significance), who carries a history of the premalignant condition that (affects) plasma cells, would warrant (further) investigation and imaging to rule out progression from precursor disease to active myeloma.

What are some of the risk factors of myeloma?

Unfortunately, we know very little of how myeloma develops, and there are limited environmental risk factors that clearly have been associated with the development of myeloma. These limited risk factors include exposure to ionizing radiation, such as Chernobyl-type radiation or exposure to benzene. There is also an association with exposure to Agent Orange. For Vietnam War veterans, that's certainly a question that needs to be asked. And there is a very slight increased incidence in first-degree relatives of patients who have had multiple myeloma or lymphoproliferative disorder. This increased risk is about two times (the risk for) the general population, and so it remains relatively small numbers and relatively small risk. We do not recommend any extra screening for first-degree family members of patients with myeloma. Studies have clearly shown, however, that multiple myeloma is basically inevitably preceded by precursor conditions. A patient who carries a diagnosis of monoclonal gammopathy of undetermined significance, this MGUS condition, or smoldering myeloma really should be monitored routinely by a hematologist/oncologist in terms of laboratory markers and physical examination to make sure these precursor (conditions) are not developing into an active cancer.

What do you usually tell patients regarding the prognosis of myeloma?

Currently, we do not consider multiple myeloma a disease that is curable. We are progressing toward a cure for many patients who have low-risk disease and can enjoy a prolonged progression-free survival that often translates into overall survival in patients in the seventh or eighth decade of life. But, biologically speaking, with current therapies we don't think

> **"I tell my patients we are getting better. We're continuing to improve and understand the biology of myeloma and the vulnerabilities of cells."** —DR. GIADA BIANCHI

that we can eradicate this disease and not have it come back over a period of 10 or 20 years. What I tell my patients is that we're getting better and better. We're continuing to improve and understand the biology of myeloma and the vulnerabilities of cells. This allows us to come up with better therapies targeting particular pathways to which myeloma cells are addicted, and so, this is a disease that is very treatable and very manageable. Many of our patients can live with myeloma for many years and decades, to an extent (similar to) a chronic illness.

What are some approved therapies that can be considered for treatment? And how can patients work with their physicians to select the right option?

We've been incredibly lucky in myeloma with the very active, highly specific therapies that have been approved over the past 15 years. We now have a category of antimyeloma therapies: proteasome inhibitors, which are medications that work by clogging the recycle bin of plasma cells. [This has been] shown in the lab to be a vulnerability intrinsic in these cells that are so exuberantly producing protein and so avidly need to discard the ones that are not properly made. We have three proteasome inhibitors that are currently FDA approved for the treatment of myeloma. We have three immunomodulatory drugs that are currently FDA approved for multiple myeloma. These are medications that are taken by mouth as pills. They have a direct toxic effect on the cells by altering certain proteins to which myeloma is addicted. But they also elicit an immune response against myeloma cells. They modulate the new microenvironment and help immune surveillance against myeloma. We have had approval of monoclonal antibodies targeting two different proteins that are expressed on the cell surface of myeloma: Darzalex (daratumumab), which targets the CD38 protein, and Sarclisa (isatuximab) with Empliciti (elotuzumab), which targets the SLAMF7 protein. These are very powerful medications; the CD38 antibodies can directly kill the myeloma cells but also engage the immune system in chasing down myeloma. We have one HDAC (histone deacetylase) inhibitor that has been approved: panobinostat for use in multiple myeloma in combination with Velcade (bortezomib) and dexamethasone. We have had approval of Xpovio (selinexor), which is the first selective inhibitor of nuclear export and has shown very promising results in highly and heavily pretreated patients. And lastly, there's Blincyto (blinatumomab fidotin). We hope that in the next few months, or maybe next few years, we're going to have approval of chimeric antigen receptor (CAR) T cells in myeloma. We think we'll may get approval of a derivative from melphalan, called Melflufen, for the treatment of myeloma. And the field of clinical trials with phase 1 molecules and first-in-human molecules is very busy. So, we expect in the years to come to have even more agents to offer our patients.

As for the second question, we can discuss a lot of the pros and cons of each category of these drugs and tailor therapy depending on the primary wishes of the patient. We have the leisure to be able to pick and choose to a certain extent.

Looking ahead a few years, how do you envision the landscape of this disease?

I think our priority now is to understand how to combine these medications together in a rational manner that is supported by laboratory work, and to discover what type of medication to prioritize or choose in patients who have certain features or certain characteristics. I think there is a lot of interest in applying multiomics approaches where we look at rearrangements in the DNA and the RNA and in the proteins to try to better understand what therapies are most appropriate for patients and how we can avoid eliciting resistance over time. I think this is going to be a big task moving ahead. The holy grail would be the ability to really understand the fundamental mechanisms that support the transformation of MGUS and smoldering myeloma into active myeloma. That would allow us to try to block the transformation from happening and therefore cure the disease before it even occurs. ■

This interview has been edited for clarity and conciseness.

Clinical Trials on Smoldering Myeloma May Open Doors to More Precision Medicine

Dr. Irene M. Ghobrial discusses this precursor to multiple myeloma, plus how patients should proceed after diagnosis and how they can participate in clinical trials. By Darlene Dobkowski, MA

DIAGNOSING SMOLDERING MYELOMA WITH a blood test is the first step to potentially preventing the progression to multiple myeloma, and a major emphasis has been placed on conducting clinical trials to learn more about the disease, according to **Dr. Irene M. Ghobrial**.

Ghobrial is director of the Clinical Investigator Research Program and Lavine Family Chair for Preventative Cancer Therapies at Dana-Farber Cancer Institute and professor of medicine at Harvard Medical School in Boston. In an interview with *CURE®*, Ghobrial discussed multiple myeloma, what patients should do after their diagnosis, how to potentially prevent progression of the condition and the importance of participating in clinical trials.

DR. IRENE M. GHOBRIAL

CURE®: What exactly is smoldering multiple myeloma?

Ghobrial: Smoldering multiple myeloma (comprises) a heterogeneous group of patients. Some patients' disease may look more like MGUS (monoclonal gammopathy of undetermined significance), and they may never progress, or they may progress very, very slowly. And some patients' disease may look more like myeloma; they progress very (quickly). This is the hardest thing (for patients) because they're given this diagnosis of smoldering (myeloma), yet they don't know which group they are in. We need better risk stratification to tell us who truly will progress in their lifetime and what to do about it.

And if I (were a patient and knew I would) likely progress to end-organ damage, meaning fractures of my bones, anemia, lytic lesions and renal failure in a couple of years, I might start considering, yes, I want early therapy to prevent progression. But if my chances of progression are only 5%, and I would progress in 10, 15 years from now, then I may want to opt for watching carefully and waiting for the new therapies, for a better precision medicine to come and not jump into treatment right now. And I think this is where we need to improve our precision. We need to be able to tell a patient in a more precise way what their true risk of progression is so that they can make decisions.

Is there anything that makes smoldering multiple myeloma different from other precursor conditions?

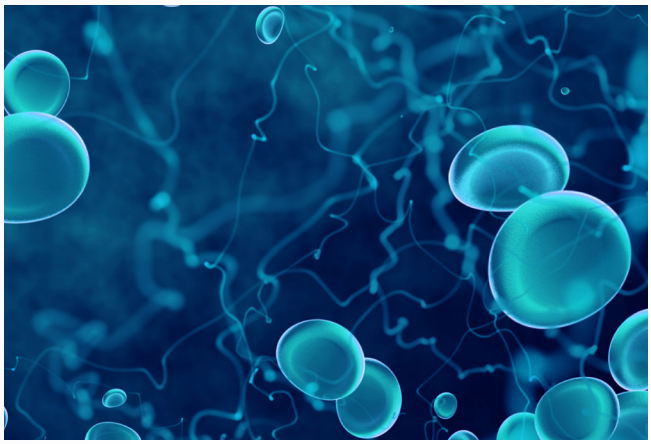
Well, the interesting thing is that we can diagnose it (easily). So, if you think about colon cancer, breast cancer, we're always trying to do cancer screening (for these diseases). We do colonoscopy, mammography, because the earlier the detection, the better, of course, the prognosis. If I can detect an early breast cancer lesion, I would be happy to get it out early and, hopefully, [the patient will] never develop breast cancer metastases. Yet all myeloma needs is a blood test.

And you think, "Why aren't we doing that? Why are we not screening for myeloma?" And that is why we have this PROMISE study. It's truly a promise to (focus on) early detection and early prevention and make a difference in the treatment of patients with myeloma.

The other thing that's important is, we know that every single patient with myeloma … likely had a precursor condition; they likely went through MGUS and smoldering myeloma but, they didn't know about it because it was not diagnosed early.

Although this specific precursor condition differs from others, can smoldering multiple myeloma differ from patient to patient?

I think that every cancer is unique in a way. And that's why we think that therapy should be unique for every patient. We should not be lumping everyone (together in) the same way. ...By the time people have multiple myeloma, there are five different subclones within one patient. Within each patient, there are five different types of cancer cells. Some may have translocations, some may have acquired this specific mutation, these may respond differently from others. And that's why when we do next-generation sequencing, which I think we should be able in the next few years to provide it to everyone, we can have that precision to actually treat patients in a different way rather than treating every (case of) myeloma the same way or every (case of) smoldering myeloma the same way. We need to be asking not only are you at high risk for smoldering myeloma? Are you going to progress? What is your biology? What are your own cancer cells tell-



ing us? Is it a p53 mutation? Is it a t(11;14) translocation?" By knowing that, we can have better precision therapy for those patients.

The other thing that we can add is the immune microenvironment. We know that the cancer cells don't live alone; they live within that host, the immune microenvironment. And now we're also teasing that apart. To truly get that idea of early therapy means you can also develop immunotherapy to prevent progression. You don't even need to use the conventional treatment we have.

Once a patient gets a diagnosis of smoldering multiple myeloma, how should they proceed?

We know that smoldering multiple myeloma is diagnosed when (a patient has) 10% plasma cells. And the first thing that I think is important is for a patient to say, "I need to go see someone who really knows what multiple myeloma does." A regular oncologist knows breast cancer, lung cancer and so many other things, but they don't truly know multiple myeloma, let alone smoldering myeloma, and what to do with it. So, I think it's important to get a second opinion. We're happy to see you anytime. We're doing virtual visits. You don't have to come all the way to Boston or to any other specialist to see us.

The second thing (that is important) is knowing your own disease, being an advocate for yourself. I think you need to know not only your percentage of plasma cells, your M65, your risk factor, but also your own biology. Patients should ask, "Can I be part of a research study? Can I be better understand my disease, make the decision for my own therapy and actively participate in the decision-making with my doctor?"

Your presentation was titled "Prevention of Progression in Multiple Myeloma." What are some ways patients can prevent this disease?

So, the first question to ask is where they are on the spectrum. Are they in the MGUS stage? Are they in the smoldering stage? And again, it's just a spectrum, so some people may be right at that edge between MGUS and smoldering. It's almost the same disease, even if you have 10% plasma cells, but you're very low risk … Or are you in the very high risk (category), almost myeloma? If so, let's think of therapy. (It's important that patients know) their spectrum of the disease, their risk stratification, their biology.

If we can do next-generation sequencing, then the next question would be (does a patient need treatment)? (We should explore if) there is an active clinical trial, which I highly encourage patients to join because I don't think we should change the standard of care yet. There are also trials that we're doing right now for patients at low risk. If a patient's status is high-risk MGUS, low-risk smoldering, we're not talking about active therapy, we're talking about exercise and fitness, intermittent fasting, metformin studies, changing personal habits and boosting fitness and exercise to help prevent progression. ... They may be some healthy habits that can help you in the early prevention.

If a patient is really in the late stages, I think these usually may not work that well. We need active therapy. And here we're trying to bring immunotherapy rather than conventional treatment to our patients.

Why is it important to have so many of these ongoing studies? And why is it also important for patients to participate?

I think it's wonderful that we have so many options, because options equal (the opportunity to) choose. … Not every patient should go on the same trial. For patients who have very high-risk cytogenetics p53 mutation or 17p deletion, I would probably err on the side of more aggressive therapy or immunotherapy. For someone who has a t(11;14) translocation, I may say, "Well, Venclexta (venetoclax) would be a wonderful drug for you."

The more trials we have, the more options we have to actually pick and choose the right option for the patient. And at the end of the day, we cannot change standard of care unless we do clinical trials, unless we have something that shows a true benefit for patients over the standard of care, which is observation or the Revlimid (lenalidomide) treatment that we have right now.

Where do you see treatment going in the next few years with the release of those results?

I hope we have something approved. The low-hanging fruit is something approved for smoldering myeloma, that we do not wait (until a patient has) lesions in their bones or anemia; renal failure does not make sense. You don't have

that in any other cancer, and you should never have that in myeloma. However, we have to be careful not to overtreat or cause toxicity. And I hope in the next few years we can get that balance; we can truly treat early without the toxicity and the too many side effects that we have in some of the therapies.

We also have an amazing opportunity to truly develop precision medicine. We have an opportunity not to repeat what we've done in myeloma, which was wonderful, but it took us 15 years to get to four drugs and more precision. Let's not repeat the same cycle for smoldering myeloma.

And I truly think that if we really want to cure patients, treat them early. We may end up knowing that answer once we actually finish the trials. And wouldn't it be amazing if we can truly say, "I have cured the patient," or someone can say, "I am cured." That's a word that we would love to see, that they're not on therapy, they don't have the disease and they're living a normal life. They can enjoy their life and not have to have the dread of constantly being on therapy, constantly thinking of their survival with multiple myeloma.

Is there anything else you'd like to tell patients?

(Consider) being an active participant in any clinical trial; some of those trials are not even therapy. They're just tissue banking, getting to know your data. You give part of your cells, part of your blood sample, for us to understand the research better. For example, the PROMISE study is part of that early screening to understand who truly has MGUS. We have PCROWD, which is (a medical research data bank for studying blood samples and analyzing data about precursor conditions) for people who have MGUS or smoldering myeloma. And, of course, if you are high risk, if you need therapy, think about what your best options are, talk to several physicians. It's perfectly fine to get a second opinion. It's perfectly fine to be empowered with your own data before you start any active therapy. And again, it's really the discussion between the physician and the patient that will come up with the best treatment option. I think that's the art of medicine that we have in multiple myeloma. ■

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