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Conference Report

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- Addressing Dose Reductions, Side Effects
- Choosing the Best Therapy in Multiple Myeloma
- Understanding MPN Symptoms
- Differentiating Between MPN Subtypes

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To Receive or Not to Receive Adjuvant Therapy?

The decision, according to Abramson Cancer Center's Dr. Naomi B. Haas, should be made collectively by a urologist, a medical oncologist and the patient. By Ryan McDonald

NOT EVERY PATIENT WITH kidney cancer should receive adjuvant therapy — the administration of additional treatment, often after surgical removal of the tumor and/or affected organ — according to an expert. **Dr. Naomi B. Haas** discussed the Food and Drug Administration (FDA)-approved adjuvant therapy options for kidney cancer and which patients are most likely to benefit from these regimens during the *CURE*® Educated Patient® Kidney Cancer Summit.

The Dilemma Surrounding Adjuvant Therapy

Adjuvant therapy, Haas explained, is often given when providers believe the patient may be at high risk for disease recurrence even after the tumor and/or affected kidney have been surgically removed.

"Ideally, we want (adjuvant therapy) to cure more patients," said Haas, director of the Prostate and Kidney Cancer Program at Abramson Cancer Center in Philadelphia. "(But) we don't want to just be giving treatment to everybody, because not all of you will need treatment." The reason, Haas added, is that not all patients face high risk of their disease returning.

DR. NAOMI B. HAAS

To determine the best treatment approach for patients, providers use a staging system that evaluates the size of the tumor, as well as whether the cancer has spread (or metastasized) to nearby lymph nodes or other parts of the body.

For instance, Haas noted that a patient could present with disease that has invaded either the veins of a kidney or the part of the kidney where the urine travels into the bladder. A patient also may see their cancer, which was completely removed, spread to a distant part of the body. Haas stressed that if the metastasis was removed several years ago and the disease eventually spread again, a provider may likely "cut it out again" and follow up with the patient periodically to ensure the cancer does not recur.

If the disease recurred or spread not long after the surgery, Haas said, the patient would be considered high risk. The problem is that there is no rule regarding who qualifies for adjuvant therapy.

"I want to emphasize that (there are) a lot of patients in any of these categories (who) can have surgery, and we can just watch (them), and (the disease) may never come back," she said. "That's one of the big things that's hard in deciding who should get adjuvant therapy."

Interest in Earlier Use of Metastatic Disease Treatments

Treatments such as Sutent (sunitinib) and Nexavar (sorafenib) have been effective in treating metastatic kidney cancer. As a result, according to Haas, providers wanted to test these therapies in other settings, including as adjuvant treatment options.

However, after years of follow-up data, many of the VEGF inhibitors that were effective in the metastatic setting showed very little activity as an adjuvant therapy. Moreover, researchers assessed these therapies in patients with metastatic disease that was completely resected. In two trials — one in Italy and the other in the United States — adjuvant treatment with these inhibitors was not superior to placebo or observation. In fact, Haas noted, a further concern about using these drugs is the presence of severe side effects.

Side effects associated with VEGF inhibitor use, according to Haas, include high blood pressure, the peeling of skin on a patient's hands, diarrhea and fatigue. "Patients who've had their kidney removed are not really excited about getting these drugs because they don't really want to feel bad after they've had their surgery, especially if they haven't had any disease present," she said.

Immune Checkpoint Inhibitors

An interesting development, Haas said, has been the emergence of immune checkpoint inhibitors (ICIs). Mostly delivered intravenously, ICIs do not directly attack the cancer. Instead, she explained, they enable a patient's immune system to fight the cancer. "That's really a good strategy, and a lot of people feel really well on these drugs," she said.

Although she referenced multiple trials in progress evaluating the efficacy and safety of several ICIs, she focused on the results of the KEYNOTE-564 clinical trial because most of the other data are not available.

In KEYNOTE-564, investigators assessed whether Keytruda (pembrolizumab) was more effective than placebo in patients following surgery. The data, presented during a medical con-

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> **"The people (who) could get adjuvant therapy, my (recommendation is that) it's really a collective decision between your urologist, your medical oncologist and yourself."**
>
> **—DR. NAOMI B. HAAS**

ference last year, demonstrated that treatment with Keytruda led to a 32% reduction in the risk of disease recurrence or death in patients.

Based on the findings, the FDA approved Keytruda in the adjuvant setting for patients with kidney cancer at either intermediate or high risk for disease recurrence. The results also indicated that treatment with Keytruda in this population was considered safe because only 20% of patients experienced severe side effects.

"But I do want to warn you with these (ICIs): A lot of us in the community are concerned because if you get a side effect from an (ICI), it can be fairly significant," she said.

For instance, Haas noted, ICIs can attack a patient's pancreas and lead to diabetes. Additionally, patients can develop arthritis as well as inflammation of the lungs or colon. "Generally, the stuff in the lungs and the colon are things that we can correct with steroids, and they can get better, but some of these other things like arthritis and diabetes can be more permanent," she said.

There remain, however, some unanswered questions about use of adjuvant therapy, according to Haas. "How long should we treat people? Is a year enough or too much? Should we give two drugs or one drug? Are we overtreating some people … or are we undertreating some patients?"

Who Should Get Adjuvant Therapy?

"Some of you don't need adjuvant therapy," she said. "But … in the people (who) could get adjuvant therapy, my (recommendation is that) it's really a collective decision between your urologist, your medical oncologist and yourself. And if you have very high-risk disease, these are the people we know probably benefit the most. And as we get (further) out and we do … real-world data with … patients not specific to clinical trials, people (who) have other health issues, I think we'll learn a lot more about these drugs." ■

Though Inherited RCC Is Rare, Genetic Testing Is Still Key to Discuss With Care Teams

Although renal cell carcinoma is rarely associated with genetic mutations, diseases like von Hippel-Lindau can be seen among patients, highlighting the need for further conversations with providers. By Kristie L. Kahl

ALTHOUGH RARE, INHERITED RENAL cell carcinoma (RCC) is important for patients to understand because genetic testing results could determine treatment options in the future, according to **Dr. Rana R. McKay**. At the CURE® Educated Patient® Kidney Cancer Summit, McKay, associate professor of medicine and urology at the University of California San Diego, offered an overview of RCC types and causes, as well as genes and genetic testing.

"Inherited RCC is rare, and there are specific guidelines for genetic testing to evaluate for inherited RCC. Most cases of RCC are sporadic and genetic testing can be considered in specific cases to inform prognosis and therapy selection," she said. "And the field is moving toward precision medicine platforms and next-generation clinical trials that will evaluate biomarker-based strategies for therapy selection."

DR. RANA R. MCKAY

RCC Subtypes and Causes

"RCC is really not just one disease. It is a cluster of different kinds of diseases that have a different reason for why they developed," McKay said.

RCC is broken into two subtypes: clear cell, which accounts for 75% of cases, and non-clear cell, accounting for 25%. Although rarer, non-clear cell RCC is broken out even further into papillary type 1 and type 2, chromophobe, translocation, collecting duct or unclassified subtypes. Meanwhile, sarcomatoid differentiation can be present across all the different histologies of RCC, McKay said. "About

20% of patients who have advanced-stage disease will have sarcomatoid differentiation in their tumor," she added.

She noted, RCC most often occurs as a sporadic cancer, caused by risk factors such as smoking, hypertension, obesity, chronic kidney disease or occupational exposures. However, RCC can also be a hereditary cancer, meaning there are inherited gene mutations that can be passed from a parent to a child.

Genetics in RCC

What makes RCC a genetic disease is an alteration that may develop within a normal kidney cell, affecting how the cell grows and divides into new cells. The main difference between inherited (or germline) mutations and acquired (or somatic) mutations, according to McKay, is that the first is present in normal DNA and the latter is present in tumor DNA. This means that inherited mutations, which account for only 5% of RCCs, are present in an egg or sperm, causing a family syndrome to be passed from parent to child. On the other hand, somatic mutations occur in nongermline tissue and are present only in the tumor. In clear cell RCC, the most common inherited alteration is von Hippel-Lindau (VHL) disease.

Genetic Testing: Germline versus Somatic

Genetic testing in the germline includes blood or saliva tests, whereas somatic genetic testing involves testing tumor tissue or blood, particularly circulating tumor DNA. McKay said people who should consider getting germline testing are:

- Those with a close relative with a known mutation in a cancer susceptibility gene.
- Those who receive a diagnosis of RCC before age 46.
- Those with bilateral or multifocal tumors.
- Those with one or more first- or second-degree relatives with RCC.
- Those with tumors that have features of hereditary RCC.

As a result of genetic testing, patients may be able to inform of cascade testing for family members, of other multidisciplinary strategies in their care and of potential targeted therapy options – like treatment with Welireg (belzutifan) for those with VHL disease.

McKay noted that somatic, or tumor, testing can be considered in patients with non-clear cell RCC and in those who are refractory to treatment to help guide their eligibility for a clinical trial. In particular, she added, this can inform a prognosis and targeted therapy strategies for patients. "It's not necessarily indicated in the guidelines for somatic tumor profiling for patients with RCC, but there are scenarios (in which) I do integrate that into my clinical practice." ■

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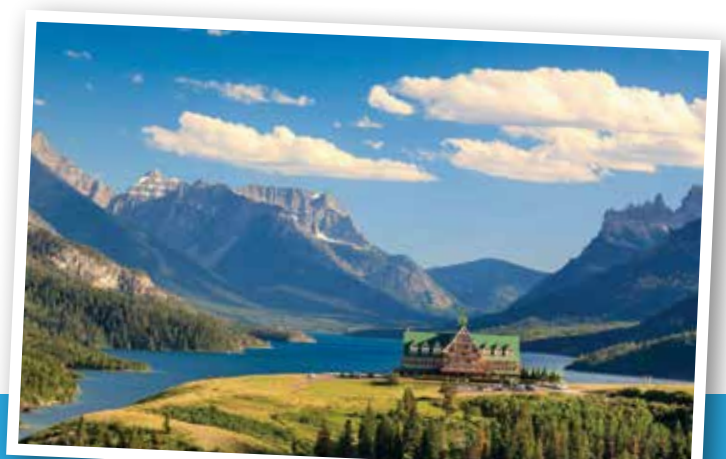

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TNM Staging: Who, What, Why and How?

An expert explains how staging can help determine whether cancer has spread, what the best course of treatment is and the likelihood of the disease returning. By Colleen Moretti

STANDARD STAGING CLASSIFICATION OF kidney cancer utilizes the acronym TNM — which stands for tumor, node and metastasis — allowing a clinician to create a treatment plan based on one's individual cancer. **Dr. Vitaly Margulis** explained why it is important for patients to understand their diagnosis better during the CURE® Educated Patient® Kidney Cancer Summit.

DR. VITALY MARGULIS

Margulis, a professor of urologic oncology at UT Southwestern Medical Center in Dallas, said the "T" tells clinicians how extensive a patient's tumor is within the kidney. The "N" indicates whether the cancer has spread to the regional lymph nodes. And "M," which he said is probably the most important part, shows whether the cancer has metastasized, or spread to other parts of the body.

"The combination of these factors determines … how to treat each individual patient. They help us to understand after treatment how to properly monitor. It also helps us understand, among other things, (whether) there (are) any preventive options or any treatments that can be given in an adjuvant fashion after surgery to prevent recurrences. In addition, this system is generally used for prognosis; based on the specifics of the TNM stage, one can speculate about the probability of the cancer coming back," he explained in an interview with *CURE*®.

In terms of tumor staging, patients can fall into four categories:

- T0: no evidence of a primary tumor.
- T1: tumor is 7 centimeters or less in dimension.
  - T1a: tumor is less than 4 centimeters.
  - T1b: tumor is greater than 4 centimeters.
- T2: tumor is 7 centimeters or greater in dimension.
  - T2a: tumor is less than 10 centimeters.
  - T2b: tumor is greater than 10 centimeters.
- T3: tumor extends into major veins or perinephric tissue (tissue around the kidney, proximal ureters, adrenal glands).
  - T3a: tumor invades the renal vein or segmental branches, pelvicalyceal system, or perirenal or renal sinus fat.
  - T3b: extends into vena cava below the diaphragm.
  - T3c: same as T3b or invades the vena cava wall.
- T4: tumor extends beyond renal fascia (connective tissue that encapsulates the kidneys and adrenal glands).

According to Margulis, staging for the nodes and metastasis only involves two or three categories. For nodes it is either NX (regional nodes cannot be assessed), N0 (cancer has not metastasized to the nodes) or N1 (cancer has metastasized to the nodes), and then either M0 (no distant metastasis) or M1 (distant metastasis).

Generally, most patients who have T1 with N0 and M0 are stage 1; T2 with N0 and M0 is stage 2. Those with T1 or T2 with N1 and M0 are stage 3, as well as those with T3 and any N0 and M0. Finally, T4 with any N and M0 or any T with any N and M1 means stage 4, Margulis explained.

"For each individual patient, the TNM stage will guide the patient and the clinicians in terms of how to manage the cancer," he said. For example, he added, stage 4 kidney cancer with metastases is treated with systemic therapies, whereas cases without metastases are treated with surgery up front — which is where the T stage is important, Margulis explained. Patients in T1 and T2 categories can generally undergo surgery that takes only part of the kidney, called a partial nephrectomy, and those in T3 or T4 categories usually undergo a radical nephrectomy to remove the whole kidney.

"You can see how understanding the exact details of TNM staging guides therapy after the treatment," Margulis said. "I think it's important that, based on TNM staging, a rational surveillance strategy is determined. Discussions can be held about availability and need for additional treatment options to minimize the probability of cancer coming back."

Because of the details about the disease TNM staging can provide patients, Margulis said it is important for them to understand and be educated on it. Additionally, knowing about different treatment options available for a specific cancer stage can create a more open, dynamic relationship with the clinician and even allow patients to think of treatment options other than the ones presented to them, he said.

"The more patients know (and) understand about their disease process, the more dynamic a patient-doctor relationship becomes. Being aware and understanding the extent of one's cancer helps understand why their physicians choose certain therapies," Margulis said. "I think it's important to be informed; it's important to question or ask specific questions about your diagnosis and staging, because I think it ultimately leads to better outcomes." ■

kidney cancer

Addressing Dose Reductions, Side Effects From IO/TKI Therapy

In a panel discussion, a physician, physician assistant and patient advocate discussed the use of immunotherapy plus tyrosine kinase inhibitors, as well as how side effects may lead to dose reductions, which is not a bad thing. By Kristie L. Kahl

AT THE CURE® EDUCATED Patient® Kidney Cancer Summit, a panel discussed the combination use of immunotherapy (IO) plus tyrosine kinase inhibitor (TKI) therapy to treat kidney cancer. **Dr. Thomas Hutson**, of Texas Oncology, who is also director of the Urologic Oncology Program, co-chair of the Urologic Cancer Research and Treatment Center at Baylor University Medical Center in Dallas, and a professor of medicine at Texas A&M College of Medicine in Bryan; **Louise Gunter**, of Texas Oncology-Baylor Charles A. Sammons Cancer Center in Dallas; and **Meryl Uranga**, a patient advocate from KidneyCAN, discussed the role of these combinations, side effects resulting in dose reductions and how taking an active part in one's care is key.

Dr. Hutson, could you offer an overview of IO/TKI combinations in kidney cancer?

Hutson: We've had modern therapy for kidney cancer now for over 20 years. There (were) two different generations, if you will, of these modern therapies. There was the original group of predominantly oral therapies like (Sutent [sunitinib], (Votrient [pazopanib], (Nexavar [sorafenib]) and (Inlyta [axitinib]). And then we saw over the past five years this newer wave of therapies that for the most part have been proven to be more active. And they include some of the newer-generation oral therapies such as (Cabometyx [cabozantinib]) and (Lenvima [lenvatinib]), as well as a whole class of drugs called immune therapies or checkpoint inhibitors.

We now have shown that we have these immune therapies that show benefit as initial (treatment) of patients with metastatic disease; we have newer oral therapies. And naturally, (because) they work differently, we know that we want to inhibit the VHL (von Hippel-Lindau) abnormalities and the angiogenesis that that brings. But now we have this role of stimulating the immune system and overcoming the immune resistance. Is there a way to combine these agents, and that has been the history of cancer care from the beginning … in other cancers, we use chemotherapy cocktails, if you will. And it's always been a belief that … it's going to be unlikely that just one single drug is going to be enough to kill a cancer, that it's probably going to take multiple drugs in a cocktail or regimen. And certainly that's what we've seen in other tumor types. So, it's natural for us to want to combine.


DR. THOMAS HUTSON

Louise, can you briefly review some of the side effects commonly associated with IO/TKI combinations?

Gunter: The main ones we see in clinic seem to be fatigue; high blood pressure; decreased appetite; nausea; thyroid problems, both overactive and underactive, but mostly underactive; we see mouth sores that can be quite painful; and cough.

Dr. Hutson, can you explain what a dose reduction is? Why do we do it? Is it a bad thing, that we must dose reduce because of side effects?

Hutson: Let me put all the myths aside. Dose reduction is not a bad thing. We give a standardized blanket dose. In many cases, it's not even weight based. It's just a standardized dose. And we should all know by now that every person is an individual and we need to adjust the dose to the individual patient's body. Some people will metabolize a drug a certain way, that (in effect) when they take one dose, they're getting a higher dose. Others get lower doses.

The only way we can figure that out — because we don't have blood tests, we're not testing drug levels — is (through) the side effects people have. In what we're achieving on our imaging studies … the biggest comfort for patients and caregivers should be that in the pivotal trials that were done, dose reductions were common. In fact, what I would consider state of (the) art … the best initial therapies that we utilize have sometimes two-thirds or more of patients on those trials requiring dose reductions.

We want to try to start everyone at full dose to let side effects declare themselves, because we would have no other way to know (whether) you're one of the 20% or 30% of patients (who) need to be at the higher dose unless we start there. And then if we do find side effects — because it is a marathon with these cancers, that we

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need to lower the dose to make the quality of life better so that people can sustain therapy — then we lower the dose.

Louise, how do you handle those conversations with the patients if there is a concern that side effects might require reducing a patient's dose?

Gunter: I just really try and assure patients that side effects are an indication that the immune system is responding to the drug. And that really, it's all about balancing the extent of the side effects with safety and quality of life.

Meryl, for others who may need a dose reduction or closer follow-up for their side effects, and based on your own experience, what is your biggest piece of advice for other patients?

Uranga: Stay very focused, stay very positive. I remember just being incredibly fearful of starting systemic treatment, because I heard a lot of stories — a lot of nightmare things, of course, from reading on the internet, etc. It can really not work in your favor. Educate yourself, become an advocate for yourself, become part of the team. Do not be intimidated or fearful of asking questions and being right on top of this stuff, and just be aware that your team is there to help you manage this.

And in many cases, including my own, you can live a very full, happy, healthy type life while still dealing with what I consider a chronic illness. I hope it's chronic for a long, long time. And I'm happy to manage those side effects. And frankly, my quality of life has sort of improved in a lot of ways because I know how important things are, like exercise and my diet. And in certain things, I've made big changes that have really improved other areas of my health. So just hang in there. Be one with your team, be educated, be an advocate, be empowered and keep kicking the can down the road. ■

multiple myeloma

Using the Best Therapies Available in Newly Diagnosed Multiple Myeloma May 'Set the Pace' for Improved Long-Term Outcomes

As triplet and quadruplet therapies help improve outcomes in patients with standard- and high-risk multiple myeloma, research is under way to understand how to best assess deep responses to these therapies. *By Darlene Dobkowski, MA*

ALTHOUGH MOST PATIENTS WITH multiple myeloma cannot be cured of their disease at the present time, an expert emphasizes the importance of using the best therapies when a patient receives a new diagnosis to destroy as many myeloma cells as possible and to potentially improve quality and quantity of life. "We have lots of new therapies down the road, but having the best response at the beginning sets that pace to make sure we give you the best shot later down the road," said **Dr. Krina K. Patel**, an associate professor in the Department of Lymphoma-Myeloma at The University of Texas MD Anderson Cancer Center in Houston, in an interview with *CURE*®. Patel discussed frontline treatment options in patients with newly diagnosed multiple myeloma during the CURE® Educated Patient® Multiple Myeloma Summit.

DR. KRINA K. PATEL

Navigating Treatment Options

With the vast availability of treatment options for patients with newly diagnosed multiple myeloma, it is important to note that the appropriate treatment is often selected by a patient's risk, which can be defined as either high risk (a missing portion of chromosome 17) or standard risk (extra copies of some chromosomes related to multiple myeloma). Other factors used to select a treatment include whether the patient has other medical issues, such as heart or lung issues, and whether they are eligible for a stem cell transplant.

Patel said that with the different regimens available to treat patients with newly diagnosed multiple myeloma, she believes the best regimen available may be the one assessed in the GRIFFIN trial: Darzalex (daratumumab), a monoclo-

nal antibody; Revlimid (lenalidomide), an immunomodulatory drug; Velcade (bortezomib), a proteasome inhibitor; and dexamethasone, a steroid.

"That group of four drugs has shown that patients can get into that really deep response over time," Patel said. "These patients on the (GRIFFIN) trial got those four cycles, which is 21 days each, then went into stem cell transplants — so these are transplant-eligible patients — and then had more maintenance (therapy) of either (Darzalex/Revlimid) or (Revlimid alone)."

Patel added that the jury is still out on whether adding Darzalex to Revlimid for maintenance therapy after a stem cell transplant is the right approach for all patients. She believed most oncologists would use Revlimid maintenance for standard-risk patients.

For high-risk patients, Patel said a quadruplet therapy is still a great option, but another option may be Kyprolis (carfilzomib), a proteasome inhibitor, plus Revlimid and dexamethasone. There have been several studies conducted assessing the benefit of that triplet therapy plus transplant. One concern about this approach is the increased risk for heart-related side effects.

Patel said patients who are ineligible for transplant are often frailer and have another type of organ dysfunction. In an attempt to not make their situations worse, there are several treatment options for these patients, but the main option most oncologists use, according to Patel, is Darzalex, Revlimid and dexamethasone, which is a triplet therapy that was assessed in the MAIA trial. This triplet therapy approach leads to fewer side effects in most patients.

"(Researchers) just showed us the five-year overall survival rates (from the MAIA trial) that are so high," Patel said. "Over time, patients are doing better and better, with their myeloma being controlled longer and longer. Now we're looking at ways to maybe take off some of the medications over time to say, 'Can we go to maintenance a little earlier?' Again … we want to get to that best response and we want to decrease toxicity."

Assessing Treatment Effectiveness

More research is also being conducted looking at minimal residual disease-negative rates, which is a measure of effectiveness of a particular treatment that indicates there was no disease detected after treatment. "That's what some of these new, up-front therapies are looking at to get more patients into that deeper response. We can't find those myeloma cells with the best technology we have right now," Patel said. "We know that leads to a better progression-free survival so myeloma stays hibernating for a lot longer."

A study published in the *Journal of Clinical Oncology* in 2021 reviewed the effectiveness of minimal residual disease–negative assessments in patients treated with Darzalex, Kyprolis, Revlimid and dexamethasone, "which is all our best drugs at the front," Patel said. Findings from the study demonstrated that high rates of minimal residual disease negativity occurred with this treatment approach.

"If we can show that if you get to (minimal residual disease) negativity, which we can do in the first six months or year of a study, and then prove that, that tells us those patients are going to do well. That would be a great surrogate marker for the (Food and Drug Administration) to use to, hopefully, in the future, help us approach trials earlier instead of taking years," Patel said.

Even with the advancements that have been made in the treatment of patients with newly diagnosed multiple myeloma, there is more in the pipeline that patients can anticipate in the next few years. "I joke with my patients all the time that if you came to me six months ago, we would have been doing this (treatment) differently," Patel said.

For example, immunotherapy, which is currently used in patients with relapsed or refractory multiple myeloma, is being assessed in earlier lines of therapy and newly diagnosed patients. "We've exponentially grown in terms of how to manipulate the immune system to help us fight the myeloma and even the antigens it goes after, not just the mechanism of action of these drugs, but how it is going to approach the myeloma," Patel said.

A Team Approach to Care

As more treatments for patients with newly diagnosed multiple myeloma become available, Patel emphasized the importance of seeing a specialist to make sure all treatment decisions are appropriate, even if that means seeking a second opinion. "It's supposed to be a team approach to make sure we get the best outcomes to all patients," Patel said. "Having that specialist in the background, (in addition to a community oncologist), can help make sure you're getting the most up-to-date treatment and making sure you need treatment."

Having an extra set of eyes on treatment options and on the patient can also be helpful when it comes to supportive medications, which can be used to counteract some of the effects of multiple myeloma therapy. "We want to make sure you're on blood thinners when you're on (Revlimid) so you don't get clots," Patel said. "We want to make sure you're on bone-strengthening medicines, because that helps keep the myeloma away and helps build your bones back if you have bone disease. We want to make sure you're on the right antiviral medicines so you don't get shingles because all these medicines can cause them. … Your doctor is going to be your doctor, who treats and takes care of everything, but we're there to make sure there's not something missing or that we change therapy if it's not working correctly." ■

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DARZALEX *FASPRO*® is a prescription medicine used to treat adult patients with 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 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 whose multiple myeloma has come back or did not respond to treatment who have received at least one prior medicine to treat multiple myeloma
- 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 pomalidomide and dexamethasone in people who have received at least one prior medicine, including lenalidomide and a proteasome inhibitor, to treat multiple myeloma
- in combination with the medicines bortezomib and dexamethasone in people who have received at least one prior medicine to treat multiple myeloma
- 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

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

IMPORTANT SAFETY INFORMATION

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

Before you receive DARZALEX *FASPRO*®, 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 *FASPRO*® 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 *FASPRO*®. 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 *FASPRO*® may harm your unborn baby. Tell your healthcare provider right away if you become pregnant or think that you may be pregnant during treatment with DARZALEX *FASPRO*®.
  - Females who are able to become pregnant should use an effective method of birth control (contraception) during treatment and for 3 months after your last dose of DARZALEX *FASPRO*®. Talk to your healthcare provider about birth control methods that you can use during this time.
  - Before starting DARZALEX *FASPRO*® in combination with lenalidomide, thalidomide, or pomalidomide, females and males must agree to the instructions in the lenalidomide, thalidomide, or pomalidomide REMS program.
    - The lenalidomide, thalidomide, and pomalidomide REMS have more information about effective methods of birth control, pregnancy testing, and blood donation for females who can become pregnant.
    - For males who have female partners who can become pregnant, there is information in the lenalidomide, thalidomide, and pomalidomide REMS about sperm donation and how lenalidomide, thalidomide, and pomalidomide can pass into human semen.
- are breastfeeding or plan to breastfeed. It is not known if DARZALEX *FASPRO*® passes into your breast milk. You should not breastfeed during treatment with DARZALEX *FASPRO*®. Talk to your healthcare provider about the best way to feed your baby during treatment with DARZALEX *FASPRO*®.

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

- DARZALEX *FASPRO*® will be given to you by your healthcare provider as an injection under the skin, in the stomach area (abdomen).

BE HEARD IN THE FACE OF A MULTIPLE MYELOMA DIAGNOSIS OR A RELAPSE.

Find your voice and learn about your options. Ask your doctor about DARZALEX *FASPRO*® (daratumumab and hyaluronidase-fihj) and if one of its regimens may be a treatment approach for you.

DARZALEX *FASPRO*® is given in **3 to 5 minutes*** as an injection under the skin.
*This refers to the injection administration time and does not account for all aspects of treatment.

It is not chemotherapy. **It's an immunotherapy** that works with your immune system to fight multiple myeloma.

Daratumumab attaches itself to the **CD38 protein** on the surface of multiple myeloma cells, as well as on certain other types of cells, such as red blood cells. Daratumumab **directly kills multiple myeloma cells** and/or allows your immune system to identify and destroy them. Because of the way daratumumab works, it may also affect normal cells.

DARZALEX *FASPRO*® may cause serious reactions, including: serious allergic reactions and other severe injection-related reactions, injection site reactions, decreases in blood cell counts, and changes in blood tests. See Important Safety Information below.

Lift your voice against multiple myeloma—prepare for your next doctor visit at **MyVoiceDarzalexFaspro.com**

DARZALEX *Faspro*®
(daratumumab and hyaluronidase-fihj)
Injection for subcutaneous use | 1,800mg/30,000units

BOLDLY YOU

- DARZALEX *FASPRO*® is injected over 3 to 5 minutes.
- 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 *FASPRO*® and after each dose of DARZALEX *FASPRO*® to help reduce the risk of serious allergic reactions and other reactions due to release of certain substances by your body (systemic).

If you miss any appointments, call your healthcare provider as soon as possible to reschedule your appointment.

DARZALEX *FASPRO*® may cause serious reactions, including:

- **Serious allergic reactions and other severe injection-related reactions.** Serious allergic reactions and reactions due to release of certain substances by your body (systemic) that can lead to death can happen with DARZALEX *FASPRO*®. Tell your healthcare provider or get medical help right away if you get any of these symptoms during or after an injection of DARZALEX *FASPRO*®.
  - shortness of breath or trouble breathing
  - dizziness or lightheadedness (hypotension)
  - cough
  - wheezing
  - heart beating faster than usual
  - low oxygen in the blood (hypoxia)
  - throat tightness
  - runny or stuffy nose
  - headache
  - itching
  - high blood pressure
  - nausea
  - vomiting
  - chills
  - fever
  - chest pain
- **Injection site reactions.** Skin reactions at or near the injection site (local), including injection site reactions, can happen with DARZALEX *FASPRO*®. Symptoms at the site of injection may include itching, swelling, bruising, pain, rash, bleeding, or redness of the skin. These reactions sometimes happen more than 24 hours after an injection of DARZALEX *FASPRO*®.
- **Decreases in blood cell counts.** DARZALEX *FASPRO*® 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 *FASPRO*®. Tell your healthcare provider if you develop fever or have signs of bruising or bleeding.
- **Changes in blood tests.** DARZALEX *FASPRO*® 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 *FASPRO*®. Your healthcare provider will do blood tests to match your blood type before you start treatment with DARZALEX *FASPRO*®. **Tell all of your healthcare providers that you are being treated with DARZALEX *FASPRO*® before receiving blood transfusions.**

The most common side effects of DARZALEX *FASPRO*® when used alone include cold-like symptoms (upper respiratory infection).

The most common side effects of DARZALEX *FASPRO*® used in combination therapy include:

- tiredness
- nausea
- diarrhea
- shortness of breath
- trouble sleeping
- fever
- cough
- muscle spasms
- back pain
- vomiting
- cold-like symptoms (upper-respiratory infection)
- nerve damage causing tingling, numbness, or pain
- constipation
- lung infection (pneumonia)
- swollen hands, ankles, or feet

These are not all the possible side effects of DARZALEX *FASPRO*®. 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 *FASPRO*®

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 *FASPRO*® that is written for health professionals.

Active ingredient: daratumumab and hyaluronidase-fihj
Inactive ingredients: L-histidine, L-histidine hydrochloride monohydrate, L-methionine, polysorbate 20, sorbitol, water for injection

Please see Brief Summary of the Product Information on the adjacent page.

cp-143282v5

janssen Oncology

PATIENT INFORMATION
DARZALEX (Dar'-zah-lex) FASPRO® (Fas-pro)
(daratumumab and hyaluronidase-fihj)
injection, for subcutaneous use

DARZALEX FASPRO may be used with other medicines called lenalidomide, thalidomide or pomalidomide. You should also read **the Medication Guide that comes with lenalidomide, thalidomide or pomalidomide if you use DARZALEX FASPRO with these medicines**.

What is DARZALEX FASPRO?

DARZALEX FASPRO is a prescription medicine used to treat adult patients with 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 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 whose multiple myeloma has come back or did not respond to treatment, who have received at least one prior medicine to treat multiple myeloma.
- 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 one prior medicine including lenalidomide and a proteasome inhibitor to treat multiple myeloma.
- 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.

DARZALEX FASPRO is a prescription medicine also used in combination with the medicines bortezomib, cyclophosphamide and dexamethasone in patients with newly diagnosed light chain (AL) amyloidosis.
It is not known if DARZALEX FASPRO is safe and effective in children.

Do not receive DARZALEX FASPRO if you have a history of a severe allergic reaction to daratumumab, hyaluronidase or any of the ingredients in DARZALEX FASPRO. See the end of this leaflet for a complete list of ingredients in DARZALEX FASPRO.

Before you receive DARZALEX FASPRO, 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 FASPRO 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 FASPRO. 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 FASPRO may harm your unborn baby. Tell your healthcare provider right away if you become pregnant or think that you may be pregnant during treatment with DARZALEX FASPRO.
  - Females who are able to become pregnant should use an effective method of birth control (contraception) during treatment and for 3 months after your last dose of DARZALEX FASPRO. Talk to your healthcare provider about birth control methods that you can use during this time.
  - Before starting DARZALEX FASPRO in combination with lenalidomide, thalidomide or pomalidomide, females and males must agree to the instructions in the lenalidomide, thalidomide or pomalidomide REMS program.
    - The lenalidomide, thalidomide and pomalidomide REMS have more information about effective methods of birth control, pregnancy testing, and blood donation for females who can become pregnant.
    - For males who have female partners who can become pregnant, there is information in the lenalidomide, thalidomide and pomalidomide REMS about sperm donation and how lenalidomide, thalidomide and pomalidomide can pass into human semen.
- are breastfeeding or plan to breastfeed. It is not known if DARZALEX FASPRO passes into your breast milk. You should not breastfeed during treatment with DARZALEX FASPRO. Talk to your healthcare provider about the best way to feed your baby during treatment with DARZALEX FASPRO.

Before you receive DARZALEX FASPRO for light chain (AL) amyloidosis, tell your healthcare provider if you have a history of heart problems. DARZALEX FASPRO should not be used in light chain (AL) amyloidosis patients with highly advanced heart disease outside of clinical trials.

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 FASPRO?

- DARZALEX FASPRO may be given alone or together with other medicines used to treat multiple myeloma.
- DARZALEX FASPRO will be given to you by your healthcare provider as an injection under the skin, in the stomach area (abdomen).
- DARZALEX FASPRO is injected over 3 to 5 minutes.
- 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 FASPRO and after each dose of DARZALEX FASPRO to help reduce the risk of serious allergic reactions and other reactions due to release of certain substances by your body (systemic).

If you miss any appointments, call your healthcare provider as soon as possible to reschedule your appointment.

What are the possible side effects of DARZALEX FASPRO?

DARZALEX FASPRO may cause serious reactions, including:

- **Serious allergic reactions and other severe injection-related reactions.** Serious allergic reactions and reactions due to release of certain substances by your body (systemic) that can lead to death, can happen with DARZALEX FASPRO. Tell your healthcare provider or get medical help right away if you get any of these symptoms during or after an injection of DARZALEX FASPRO.
  - shortness of breath or trouble breathing
  - dizziness or lightheadedness (hypotension)
  - cough
  - wheezing
  - heart beating faster than usual
  - low oxygen in the blood (hypoxia)
  - throat tightness
  - runny or stuffy nose
  - headache
  - itching
  - high blood pressure
  - nausea
  - vomiting
  - chills
  - fever
  - chest pain
- **Injection site reactions.** Skin reactions at or near the injection site (local), including injection site reactions, can happen with DARZALEX FASPRO. Symptoms at the site of injection may include itching, swelling, bruising, pain, rash, bleeding, or redness of the skin. These reactions sometimes happen more than 24 hours after an injection of DARZALEX FASPRO.
- **Heart problems in people with light chain (AL) amyloidosis**. Heart problems, in some cases fatal, have occurred. Your healthcare provider will monitor you closely during treatment with DARZALEX FASPRO. Call your healthcare provider right away if you get any of the following symptoms: chest pain, feeling faint, swollen legs, shortness of breath, or abnormal heart rhythm.
- **Decreases in blood cell counts.** DARZALEX FASPRO 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 FASPRO. Tell your healthcare provider if you develop fever or have signs of bruising or bleeding.
- **Changes in blood tests.** DARZALEX FASPRO 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 FASPRO. Your healthcare provider will do blood tests to match your blood type before you start treatment with DARZALEX FASPRO. **Tell all of your healthcare providers that you are being treated with DARZALEX FASPRO before receiving blood transfusions.**

The most common side effects of DARZALEX FASPRO when used alone include cold-like symptoms (upper respiratory infection).

The most common side effects of DARZALEX FASPRO used in combination therapy include:

- tiredness
- nausea
- diarrhea
- shortness of breath
- trouble sleeping
- fever
- cough
- muscle spasms
- back pain
- vomiting
- cold-like symptoms (upper-respiratory infection)
- nerve damage causing tingling, numbness or pain
- constipation
- lung infection (pneumonia)
- swollen hands, ankles, or feet

These are not all the possible side effects of DARZALEX FASPRO.

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 FASPRO.

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

What are the ingredients in DARZALEX FASPRO?

Active ingredient: daratumumab and hyaluronidase-fihj

Inactive ingredients: L-histidine, L-histidine hydrochloride monohydrate, L-methionine, polysorbate 20, sorbitol, 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.DARZALEXFASPRO.com.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 7/2021

cp-145255v4

multiple myeloma

From All Sides: Treating Multiple Myeloma as a Chronic Disease

In a panel discussion, a patient and her caregiver share their experiences, while a nurse navigator and a medical oncologist discuss the long-term treatment of multiple myeloma as a chronic disease. By Kristie L. Kahl

HAVING A SUPPORT GROUP and seeking out second opinions are key to a more successful care journey for patients with multiple myeloma. **Donna and Jack McNutt** shared what their journey has been like as a patient and caregiver during a panel at the CURE® Educated Patient® Multiple Myeloma Summit, also featuring **Dr. Noopur Raje**, of Massachusetts General Hospital, and **Grace Allison**, of the Multiple Myeloma Research Foundation, who shared their advice on long-term treatment of the disease.

DR. NOOPUR RAJE

Donna, can you tell us about your journey with myeloma and what it has been like to achieve your treatment milestones throughout?

Donna McNutt: In 2015, I was diagnosed in the last stage of multiple myeloma, with failing kidneys. I had a stem cell transplant at City of Hope National Medical Center and have never been out of treatment. I think I've been on every type of treatment. This past October, I was given the opportunity to have chimeric antigen receptor (CAR)-T cell therapy. I sit before you today, seven years after a rather traumatic beginning of my journey, to give hope to other patients. There have been so many wonderful new treatments available to me. I've done wonderful after CAR-T (cell therapy), and for the first time in seven years, I (have been) completely off treatment since October.

> **"I sit before you today, seven years after a rather traumatic beginning of my journey, to give hope to other patients. There have been so many wonderful new treatments available to me."**
>
> *—DONNA MCNUTT*

Jack, can you discuss your role as Donna's caregiver and what that journey has been like for you?

Jack McNutt: I've been by her side 100%, going to every appointment, doing a deep dive into all aspects of myeloma and its treatments, the test results … and just being there, keeping a positive outlook. … I sort of had that from day one … let's keep moving one day at a time, one week, one month. Let's not become pessimistic. … There's so many studies being done and new treatments are going to emerge every month, every year. Let's keep going. Case in point with the CAR-T cell infusion Donna had, which is remarkable.

Dr. Raje, can you discuss how we're treating myeloma more as a chronic disease nowadays? How do we decide on a patient's treatment plan?

Raje: It's important to remember every patient with multiple myeloma is different. And it's important that we try and cater to what is going on with that specific patient. … What we can do in 2022 is look at myeloma in the long-term and try to come up with treatment strategies so you have all your options available to you.

The important thing to remember is myeloma can relapse. When I start talking to my patients, I will always tell them whatever we do right now, we're going to make sure we're not burning any bridges down the road so that you will have access to drugs that come along the way. (Right now), we're doing combination approaches to begin with, then dose adjusting, depending on how you tolerate them. Typically, we'll keep readjusting based on when the disease comes back.

Grace, can you discuss how nurses play a role in the treatment continuum?

Allison: It's important, as we've been hearing all along, that

an educated patient can make better choices in terms of their health care. We want to be able to provide information on how to manage side effects … and then transitioning into survivorship mode, letting them know this is a chronic condition we can live with. So addressing those survivorship issues, such as long-term care and possibly other health issues.

Dr. Raje, why is treating with the most effective treatment first recommended now?

Raje: It's important to not save the best for last. You've got to use your best drugs up front. We have lots of new drugs available to us.

The other important thing to remember, as we're progressing through the journey of myeloma, is that how we approach myeloma keeps changing. A couple years back, we used three-drug combinations. Today, I would use a four-drug combination.

It's critical to try to get a patient into remission — as deep of a remission as possible. If you can get to (minimal residual disease) negativity, you need to do that because the deeper your response, the more delayed your disease coming back will be. … (If) we can keep you well, that should be the goal. (We shouldn't) use the mentality of "I'm going to save this for when the disease comes back." The one thing I will say is when we're using the drug combinations, on average, the disease doesn't come back for four or five years now. That is remarkable. That's a little bit of a shift from what was happening early on.

Donna, looking back on your diagnosis, what is one thing you wish you knew about having an active voice in your journey that you know now?

Donna McNutt: The biggest thing … (going into my multiple myeloma), was being sure I knew I needed to get a second opinion. … I meet a lot of patients who are staying local (for their treatment), and I (encourage) them to find a specialist in their cancer.

What I would also tell other patients … is that you'll find your footing. It's a lot in the beginning. … That's what I would assure a patient. … You'll find what works for you. The combination I have in my life now works for me. That's what I would tell myself. You're going to find the right way to be on this path. Don't be hard on yourself.

Jack, from a caregiver perspective, why is it important for your voice to also be heard through this journey?

Jack McNutt: Well, because I'm right along with her and I'm seeing it. I'm seeing the side effects she has, (as well as) the hope or the doubt that she goes through. I can provide that second voice to say, "Hey, wait a minute." So it's not just coming from her. It's (also) coming from somebody who's watching her very closely.

> **"There's so many studies being done and new treatments are going to emerge every month, every year. Let's keep going. Case in point with the CAR-T cell infusion Donna had, which is remarkable."**
>
> ***—JACK MCNUTT***

Grace, do you have recommendations or resources you can share?

Allison: My role is a patient navigator at the Multiple Myeloma Research Foundation. We are a group of patient navigators who can be available by email or telephone. If patients have questions from initial diagnosis on, and at any point in their myeloma journey, we're there to be a sounding board, to be objective, to empower that patient to be able to advocate for themselves and to get the care they need. So (talk to) navigators and support groups. When you are initially diagnosed, it's such a new and foreign world, (so you need) to find a support group.

On our website, we have a function where you can search by just putting in your zip code to find a support group in your area. You can choose one that fits you. We have myeloma mentors available, who are specially trained and available to connect with patients at any point to offer that support so people do not feel alone. ■

This panel transcription has been edited for clarity and conciseness.

multiple myeloma

Tailored Treatments for Relapsed/Refractory Multiple Myeloma May Help Patients Attain Better Outcomes

Combination therapies and advances in the treatment of patients with relapsed or refractory multiple myeloma offer patients hope as they navigate this chronic disease. By Darlene Dobkowski, MA

ALTHOUGH A DIAGNOSIS OF relapsed or refractory multiple myeloma can be alarming for patients, families and caregivers, hope continues to grow as more treatment options become available, including combination therapies. These therapies help patients attain long-standing remissions and controlled disease and allows them to have improved quality of life.

"It's important that patients have hope when they're diagnosed with this illness," said **Dr. Noa Biran**, an associate professor of medicine in the Division of Multiple Myeloma at the John Theurer Cancer Center at Hackensack University Medical Center in New Jersey, in an interview with *CURE*®. "It's a very scary, life-changing event. They hear the word 'cancer,' and they think it's the end but it's not. It's important to emphasize that multiple myeloma is a chronic disease. It is a disease that is characterized by many relapses and remissions, and chronic treatment and continuing on treatment can keep the disease in remission for decades." Biran discussed treatment advances for patients with relapsed or refractory multiple myeloma during the CURE® Educated Patient® Multiple Myeloma Summit.

DR. NOA BIRAN

Therapies Approved by the Food and Drug Administration

There are several therapies that have been approved by the Food and Drug Administration for the treatment of multiple myeloma, including the following:

- Immunomodulatory drugs, such as Revlimid (lenalidomide), Thalomid (thalidomide) and Pomalyst (pomalidomide).
- Proteasome inhibitors, such as Velcade (bortezomib), Ninlaro (ixazomib), Kyprolis (carfilzomib) and chemotherapy/alkylators (melphalan, bendamustine, cyclophosphamide).
- Histone deacetylase inhibitors, such as Secura (panobinostat).
- Monoclonal antibodies, such as Darzalex (daratumumab), Empliciti (elotuzumab) and Sarclisa (isatuximab).
- B-cell maturation antigen–directed therapies, such as Blenrep (belantamab, ide-cel).
- XPO inhibitors, such as Xpovio (selinexor).

Despite the availability of these drugs, Biran noted that treatment decisions should not be made on a one-size-fits-all basis. "Treatments are tailored to each individual patient based on their prior response to therapy, their comorbidities and their social situation," she said. "It's important to use your best treatments in the beginning of the disease, not wait and save them for later."

Using the best treatments up front, including combinations, can be helpful, especially since multiple myeloma is a very heterogenous disease, meaning it can have several root causes, Biran said. For example, one patient can have different tumors, such as a lesion in the bone, a lesion in the ribs and a lesion in the clavicle. "In one patient, you can have three different types of multiple myeloma based on the genetics of the disease," she said.

Biran also emphasized the importance of using multiple agents together to treat multiple myeloma. "You're more likely to achieve durable and long-lasting remissions when you combine many agents together," she said. "The best ones you have that are the most potent and effective, the more likely you are to (target) all the different clones of the disease and prevent further mutations of the disease and resistance. You don't want to end up with resistant myeloma that's going to grow into what we call extramedullary myeloma, or disease outside of the bone marrow, because then you're dealing with a very different disease."

At diagnosis or relapse, some patients worry about whether they'll be able to continue living their life and manage their disease, especially during treatment. Biran said the side effects of multiple myeloma treatments are almost always manageable, and some people even work through treatment.

"It's rare to have a side effect where you have to stop the treatment altogether," Biran said. "One example of that is a type of severe rash that can occur with … lenalidomide or pomalidomide, where there can be a severe rash and they're allergic to the treatment, or a cardiac event or something of that nature. But for the most part, we can reduce, we can hold and we can give treatment breaks. If it's a pill, we'll do one week on, one week off and give a different schedule."

Approaches to Treating Relapsed/Refractory Multiple Myeloma

Biran added that treating patients with relapsed multiple myeloma is different compared with those with newly diagnosed disease. "This is a marathon; it's not a race in the relapsed setting," Biran said. "In the newly diagnosed setting, you push through because you want to maybe get to transplant, and you want to give a high dose to get the treatment in as much as possible," Biran said. "But in the relapsed setting, we're talking chronic, so your goal is not always to get to zero. If you can, great. But if you cannot, it's OK to have some remaining disease, as long as the treatment is tolerated and the person can have an excellent quality of life."

Although treatment is focused on the disease itself, it's important for patients to focus on their well-being during treatment, especially since treatment can take a toll on a patient regardless of its form. "It's important to have a different perspective in life and to try to treasure each and every day," Biran said. "You must make sure you're caring for yourself every day, … you're putting yourself first, you're exercising minimizing steroid-related toxicity to the muscles, minimizing stress and eating healthy so you can tolerate the treatment and enjoy your time."

In addition to self-care, Biran highlighted the importance of open communication with a patient's doctor throughout treatment. "Find a provider you trust," she said. "Have active discussions with your doctor, tell them about side effects and discuss alternatives. Whenever a treatment is offered, it's always a good idea to ask, 'What are my alternatives? Are there clinical trials available to me?'"

Biran mentioned that throughout treatment, remissions and other times related to relapsed or refractory multiple myeloma, patients should continue to live their lives. "Don't let the disease get in the way of your life," she said. "I tell my patients this: We're not treating the numbers on the page, the M spike — that's not my goal. It's you. You're the person and the goal of this, so you can see your grandchildren and you can go on vacation. (In a way) treatment should be worked around life, not life worked around treatment." ■

MPN Symptoms Overlap Between Diseases

The challenge with myeloproliferative neoplasms is that not one particular symptom is best associated with a particular disease, said one expert. By Ryan McDonald

MYELOPROLIFERATIVE NEOPLASMS (MPNS) — a group of blood cancers — may often present in patients who may develop a variety of symptoms that don't always come from one place.

The challenge, according to **Dr. Aaron T. Gerds**, is that these occurrences of symptoms from various causes can create a complex story for patients who are diagnosed with polycythemia vera, essential thrombocythemia and myelofibrosis — all of which are classified as MPNs.

DR. AARON T. GERDS

Gerds, deputy director for clinical research at Cleveland Clinic Taussig Cancer Institute in Ohio, recently discussed how oncologists diagnose MPNs and how certain symptoms may play a role in how they determine which disease a patient has during CURE®'s Educated Patient® MPN Summit. "We tend to see more vascular events, meaning blood clots, in patients with polycythemia vera and (essential thrombocythemia) than in myelofibrosis," Gerds said during the presentation. "We know controlling the hematocrit (percentage of red blood cells in the blood) … can reduce the risk of having blood clots. Sometimes this … can be unrecognized. So (individuals) can have (an unrecognized MPN), then ultimately have a clot even before their diagnosis."

How Providers Make a Diagnosis

First, Gerds noted, health care providers perform a medical history and clinical examination on their patients. Labs are collected to review basic blood counts and to see whether there are any makers for infectious diseases.

For instance, he said, they are looking to see whether a patient may have had hepatitis in the past that they weren't aware of.

"That way, when we do use treatments later on, we can avoid complication," Gerds said.

After these tests are performed, a bone marrow biopsy is collected.

"We want to go to the source (and) see abnormalities, (which is) the bone marrow," he said.

Additionally, a pivotal piece to the puzzle of diagnosing an MPN is the use of molecular testing, according to Gerds. This process has become the "centerpiece in making the diagnosis," he said. The reason being that mutations to the JAK2, calreticulin and MPL genes are very common in patients with these disorders. For example, polycythemia vera is often considered to be the case in patients if they have elevated bone marrow counts, as well as the presence of a JAK2 mutation, which is present in upward of 95% of patients, according to Gerds.

MPNs Are Cancer

Before discussing the common symptoms that occur in patients with MPNs, Gerds reiterated to the audience that MPNs are a type of cancer.

"These mutations have occurred, (which) has led to abnormal growth of cells," he said. "Therefore, we do classify this as a type of cancer. Since it is a cancer of the blood and bone marrow, we classify this as a type of leukemia. Although it is a chronic leukemia, meaning patients can live many years, even without treatments."

However, this notion is a stark contrast to patients who develop acute leukemia. Gerds noted that acute leukemia tends to be significantly more aggressive than a chronic leukemia, such as MPNs.

No 'Discrete Bins'

The symptoms patients may experience don't always fall into discrete bins, which means there's a tremendous amount of overlap between the diseases that make up MPNs, Gerds explained.

For instance, splenomegaly, or an enlarged spleen, is common in patients with myelofibrosis and is often used as a diagnostic criterion in patients. However, Gerds said that approximately one-third of patients with polycythemia vera will have an enlarged spleen.

"(This) can cause pain and discomfort in the abdomen (and) shortness of breath if (the spleen) pushes on the diaphragm. It can (also) press on the stomach and (individuals may) have early satiety, meaning they fill up right away when they eat, even leading to weight loss," he said.

The problem is that pain doesn't always mean a patient has an enlarged spleen, Gerds explained. There are times when a patient may have a smaller spleen but may also be experiencing pain and discomfort in that area. This is

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why providers should take a good inventory of patient's symptoms, he noted.

Significant Symptom Burden

In addition to early satiety and abdominal discomfort, patients may experience fatigue, inactivity, issues with concentration, night sweats, itching, bone pain and fever.

These symptoms can also be present at the time a patient presents to the provider before their diagnosis.

Polycythemia vera is usually associated with a significant symptom burden in patients, Gerds highlighted.

"Just because you have polycythemia vera or (essential thrombocythemia) doesn't mean you're any less symptomatic than someone who has myelofibrosis," he said.

Moreover, people should be aware of a certain symptom that is unique to polycythemia vera.

According to Gerds, "the most famous" symptom of polycythemia vera is aquagenic pruritus, or the occurrence of itchy skin after a hot shower. "(It) tends to be more on the trunk and central in the body, and then less common in the periphery," he said. "But this is kind of a classic symptom we often talk about in polycythemia vera and can be an early tip-off to a diagnosis of the disease."

Take-Home Message

Gerds said the purpose of his talk was to provide a basic foundation for what MPNs are.

The main message, he noted, is that polycythemia vera, essential thrombocythemia and myelofibrosis are very similar, and most symptoms tend to overlap across the diseases.

"We take (the patient's) disease risk, how big their spleen is (and) what symptoms (they) are having, and (we) use all that information to help apply the best treatments for that patient," he said. ■

Differentiating Between MPN Subtypes Is 'Not Always Black and White'

The difference between two types of MPNs, prefibrotic myelofibrosis and essential thrombocythemia, is not always easy to distinguish, but it is essential that patients know which disease they have. *By Brielle Benyon*

WHEN RECEIVING A DIAGNOSIS of a myeloproliferative neoplasm (MPN), it is crucial — although at times difficult — to come to the proper diagnosis. This is especially true when differentiating between two subtypes of the disease, prefibrotic myelofibrosis and essential thrombocythemia, according to Dr. Jamile M. Shammo, professor of medicine and pathology at Rush University Medical Center in Chicago.

DR. JAMILE SHAMMO

"At times, arriving at the right diagnosis is not necessarily a simple black-and-white type (of) thing. We as physicians and patients need to deal with some degree of uncertainty and understand MPNs have some degree of spectrum that we have to be comfortable with. With that in mind, we (must) also be cognizant of various diagnoses and diagnoses that may carry (varied prognoses) with them. It's important to understand that," Shammo said during CURE®'s Educated Patient® MPN Summit.

All subtypes of MPNs occur when the bone marrow is hypercellular, meaning it produces too many cells. If a patient has elevated blood counts, clinicians will first want to rule out other potential causes, such as inflammation, infection or iron deficiencies. After that, patients may undergo next-generation sequencing that could reveal a JAK mutation, which is highly indicative of MPNs.

Once it is determined that a patient does have an MPN, clinicians may look at the characteristics of the cells in the bone marrow to help determine what kind of MPN it is.

Nowadays, there is more of an emphasis and research toward identifying essential thrombocythemia versus prefibrotic myelofibrosis, but that was not always the case.

Shammo explained that in the 1970s, researchers started to analyze the different outcomes in patients who were all diagnosed with essential thrombocythemia. They found

that some had only elevated megakaryocytes (cell clustering in the bone marrow that is common in MPNs), whereas others also had an increased amount of granulocytes (a type of white blood cell).

"They thought … if we applied a certain new designation (to patients labeled as having essential thrombocythemia), specifying those particular morphologic features, can we separate those patients into true essential thrombocytopenia and those who may fall into the category of prefibrotic myelofibrosis?" Shammo said.

An essential thrombocythemia diagnosis is fairly straightforward, with the following criteria:

- Platelet count over 450.
- Other types of MPNs or myelodysplastic syndrome are excluded.
- Evidence of a clone in the presence of a driver mutation
- Megakaryocytic proliferation.
- Little fibrosis in the bone marrow.

"This is essential to how patients (with essential thrombocythemia) should be diagnosed — by exclusion and by demonstrating that the bone marrow has very little fibrosis and just megakaryocytic lineage proliferation," Shammo said.

On the other hand, coming to a prefibrotic myelofibrosis diagnosis can be "a little more complicated, because you have to show that the megakaryocytes are proliferating and have granulocyte proliferation," Shammo said.

Additionally, prefibrotic myelofibrosis tends to come with anemia that cannot be explained by any other condition.

Even within the subset of patients who have prefibrotic myelofibrosis, there are different categories that can determine what kind of treatment they undergo. Those with low risk may be eligible for observation only, whereas those with intermediate risk (those with estimated survival averages of 10 years or more) can have their therapy focus on symptoms and perhaps consider participation in clinical trials. However, those with high-risk disease (with an estimated average survival time of less than five years) will have intensive treatment, potentially stem cell transplant or clinical trial participation.

Although difficult, differentiating between essential thrombocythemia and prefibrotic myelofibrosis is important, because the two can come with vastly different outcomes. Shammo noted that prior research found that prefibrotic myelofibrosis tended to be more likely to progress to overt myelofibrosis and have poorer leukemia-free survival rates.

"Prefibrotic myelofibrosis has a better prognosis than those who have full-blown primary myelofibrosis, but it's a bit worse than those patients who have (essential thrombocythemia)," she said. ■

'Thrilling' Updates May Improve Myelofibrosis Outcomes in the Near Future

The disease tends to have poor outcomes and quality of life, but new treatments may change that over the next few years, an expert explained. *By Brielle Benyon*

MYELOFIBROSIS TENDS TO HAVE a poor prognosis and high symptom burden compared with other types of myeloproliferative neoplasms (MPNs). However, up-and-coming treatments will hopefully increase survival and improve quality of life in patients with the disease, explained **Dr. Srdan Verstovsek**, a professor of medicine in the Department of Leukemia at The University of Texas MD Anderson Cancer Center in Houston, Texas.

At the CURE® Educated Patient® MPN Summit, Verstovsek discussed what's on the horizon for patients with myelofibrosis.

DR. SRDAN VERSTOVSEK

"Myelofibrosis is the deadliest (MPN). (The) average survival is (approximately) five to seven years, and much is needed to change that outcome," Verstovsek said in an interview with *CURE®*.

JAK Inhibitor Combinations

Currently, myelofibrosis is treated by inhibiting the JAK/STAT pathway, which leads to inflammation. There are three Food and Drug Administration (FDA)-approved drugs that do this: Jakafi (ruxolitinib), Inrebic (fedratinib) and Vonjo (pacritinib). Although these drugs work to improve quality of life and help patients to potentially live longer, they work for only an average of approximately three years, highlighting the need for further lines of treatment, according to Verstovsek. ▸

"Still, we (must) make a major change in the overall outcomes by possibly adding medications to JAK inhibitors, or for when they don't work anymore," he said.

Although JAK inhibitors are more generalized and do not target a specific mutation, phase 3 trials are investigating whether the addition of other drugs, such as navitoclax, pelabresib or parsaclisib, can help Jakafi work better or longer.

When JAK Inhibitors Stop Working

When myelofibrosis completely stops responding to JAK inhibition, "we still have a symptom problem, we still have spleen (enlargement), and we still have anemia, but it's much worse and life is short. There are therapies (being studied), such as navtemadlin to control the symptoms and imetelstat to prolong the lives of these patients," Verstovsek said.

Navtemadlin (KRT-232) is a new drug that is being explored in this setting. It inhibits MDM2, which is a gene that is important in cancer cell survival.

Imetelstat, on the other hand, inhibits the enzyme that maintains the DNA at the end of chromosomes when cells divide. Without this DNA, the cells cannot proliferate, and they end up dying.

"Within the next three years, we'll have (several) combinations and options to give our patients," Verstovsek said.

Targeting Bone Marrow

Myelofibrosis occurs in the bone marrow, so one new treatment strategy is looking at how to attack the disease where it occurs.

PRM-151 is a novel drug that inhibits the differentiations of blood cells. It prevents monocytes from becoming fibers, which can lead to myelofibrosis — hence "fibrosis" in the disease name.

"If you can tackle the fibers or understand the microenvironment where that happens, (then) that would be another angle of helping these patients," Verstovsek said.

Although the drug reversed fibrosis in preclinical models, it is still far off from gaining FDA approval for the treatment of humans.

Looking Ahead

Ultimately, Verstovsek is hoping that upcoming years will bring better, more targeted therapies to patients with myelofibrosis.

"(Although) there are hopes about reaching that stage where we can work on the DNA itself, it's much more realistic that over the next few years, we are in a situation to start talking about targeting malignant cells by virtue of identifying a marker on them to distinguish them from normal cells and be much more successful in (treatment)," he said.

Although JAK inhibitors are still the mainstay, up-and-coming approvals can make their use even better.

"It is quite thrilling to expand where we are with JAK inhibitors, improving quality of life, maybe making people live longer for a few years, but then also talking about new drugs that are close to approval," Verstovsek said. ■

Novel Agents Are on the Horizon for Polycythemia Vera

An MPN expert discusses therapies in the pipeline for treating polycythemia vera.

By Colleen Moretti

TREATMENT IS CONTINUING TO advance for patients with polycythemia vera, with a new focus on reducing symptom burden, according to **Dr. Angela Fleischman**, associate professor in the Division of Hematology/Oncology at the University of California, Irvine. Fleischman presented further on this topic at the CURE® Educated Patient® MPN Summit.

A current area of interest in polycythemia vera, she explained, is reducing the hematocrit (red blood cells) without increasing the risk of thrombosis or making patients iron deficient. "This is clearly an area of need for polycythemia vera," she said, adding that keeping the hematocrit levels below 45 will reduce risk of death from cardiovascular causes or major thrombotic events in patients with the disease.

DR. ANGELA FLEISCHMAN

She further explained about a protein called hepcidin, which is important for the body to utilize the iron it has. In polycythemia vera, when people have too much blood, hepcidin could increase and be made so that although the body has iron, it cannot make red blood cells.

Therefore, this is now the focus for new, novel agents in the polycythemia vera space.

"The rationale for utilizing these agents that either mimic (or upregulate) hepcidin are based on the idea that (although) somebody is getting a phlebotomy, the hematocrit is only checked once in a while. So (although patients) are phlebotomizing for their hematocrit, when it is seen below 45, (the patient) is probably spending a significant amount of time that isn't adequate, or above 45 because it hasn't been checked, and iron deficiency is a real issue in polycythemia vera," she said.

Fleischman highlighted two novel agents currently under investigation for the treatment of polycythemia vera: rusfertide (PTG-300) and a compound called ISIS 702843.

"The central goal (of both) is to increase hepcidin so a (polycythemia vera) patient's body cannot use the iron to make red blood cells, and they do it in two different ways," she said.

Rusfertide is a drug made to look like hepcidin to the body, she explained, and is currently far along in clinical trials. At the 2021 American Society of Hematology Annual Meeting and Exposition, it was presented that rusfertide controlled hematocrit and eliminated the requirements for phlebotomy in patients with polycythemia vera.

The ISIS compound increased hepcidin in a different mechanism, Fleischman explained. This agent utilizes the liver to help increase the production of hepcidin.

"That's sort of complicated, but to make it less complicated, it (basically) gets rid of an inhibitor of hepcidin so it will increase the body's natural production of hepcidin," she said.

Earlier Development

Fleischman also discussed two other treatment approaches currently under early development in her personal lab: a healthy diet approach to reduce inflammation in patients with myeloproliferative neoplasms (MPNs), including polycythemia vera.

"The reasoning is that (patients with an) MPN, including patients (with polycythemia vera), can have increased inflammation, (which) can contribute to many of their symptoms," she said, adding that this would be a low-cost treatment option for patients.

There have been two pilot studies that demonstrated the utilization of a Mediterranean diet, which is rich in anti-inflammatory compounds, in patients with MPNs can be beneficial. Next steps will include a larger study that will evaluate the symptom burden reduction in association with diet.

She also mentioned the antioxidant N-acetylcysteine, which has already been used for many years as an antidote for Tylenol overdose and has been made available for over-the-counter use.

"Our first step with this agent is to identify the appropriate dose of N-acetylcysteine for patients with MPNs. So, we currently have an open and optimal dose finding study of N-acetylcysteine in patients with MPNs," she said. ■

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