TOP MYELOMA HITS

CLINICAL PEARLS, BEST PRACTICE TIPS FOR YOUR PRACTICE

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The number of available treatments for the newly diagnosed patient with multiple myeloma has increased. As a result, clinical outcomes are improving. With more therapies to choose from, finding the best initial regimens and drug combinations for each individual patient can be a challenge. In this issue, oncology specialists discuss how they hit on the right therapeutic strategy in the expanding space of multiple myeloma treatments. They also share their diagnostic approaches and top tips on patient and practice management.

Multiple Myeloma Diagnosis

We start with the basic lab testing, like CBC, renal function, bone panel," says Enas Y. Mutahar, MD, a myeloma specialist at a tertiary center in Dammam in the eastern province of Saudi Arabia. "Then if we have the suspicion based on the clinical and initial assessment, we proceed with serum protein electrophoresis, urine protein electrophoresis and immunofixation of both. We do have the free light chain assay performed in our lab, as well as bone marrow biopsy **(Figure 1)**, flow cytometry, fluorescence in situ hybridization (FISH) cytogenetics, together with all the imaging studies, including positron emission tomography computed tomography (PET-CT)."

Majed Alahmadi, MBBS, FRCPC, ABIM, says it is the same scenario at the Princess Noorah Oncology Center in Jeddah, Saudi Arabia, where he is Assistant Professor, Consultant Adult Hematology/BMT, and Fellowship Training Program Director. "We have all of these available tests. And based on the clinical suspicion, we would request further testing. Most myeloma cases are referred to us by either internal medicine, nephrology, or orthopedics. Usually, the starting point is anemia, renal failure, or lytic lesions, pathological structures, which will lead to the diagnosis of myeloma."

"Unfortunately, sometimes we get myeloma in later stages, for example, end stage renal failure on dialysis or multiple fractures, where it was not was not up front from the beginning," says Dr. Alahmadi.

"This is one of the things that we are working on in Saudi Arabia: increasing the awareness of non-hematologists about myeloma, so they can suspect it early and refer the patient."

Adriana Rossi, MD, Assistant Professor of Medicine in the Division of Hematology and Medical Oncology Associate Clinical Director of the Myeloma Center at Weill Cornell Medicine in New York City, New York, says that is similar in the United States, "a lot of diagnosis is educating physicians who may not have myeloma on their radar."

Use of FISH, CT, and PET

Ayman Alhejazi, MD, Head, Division of Adult Hematology/Oncology in the Department of Oncology in

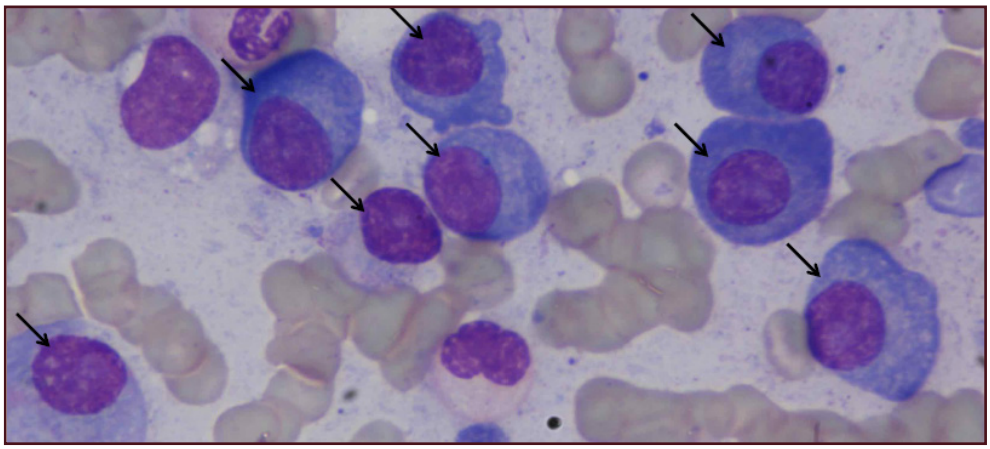

Figure 1. Bone marrow aspirate from patient with multiple myeloma diagnosed per the standard guidelines.

Slide shows plasma cells in Jenner-Giemsa stain at 1000x magnification. (Source: Gupta R, Gupta A. MiMM_SBILab Dataset: Microscopic Images of Multiple Myeloma [Data set]. The Cancer Imaging Archive. 2019. Open Access. https://doi.org/10.7937/tcia.2019.pnn6aypl)

> Unfortunately, sometimes we get myeloma in later stages, for example, end stage renal failure on dialysis or multiple fractures, where it was not diagnosed, or the suspicion of myeloma was not up front from the beginning. This is one of the things that we are working on in Saudi Arabia: increasing the awareness of non-hematologists about myeloma, so they can suspect it early and refer the patient."
>
> — Majed Alahmadi, MBBS

the King Abdulaziz Medical City, Riyadh, Saudi Arabia, says their approach is not that much different from everyone else. "After clinical suspicion of multiple myeloma in a patient, we do a battery of tests to diagnose multiple myeloma and to know the prognosis of each. We do serum protein electrophoresis, urine protein electrophoresis, immunofixation, serum free light chain ratio, beta-2 microglobulin, albumin, LDH, and then a bone marrow biopsy to confirm our diagnosis. We do FISH testing in every patient upon diagnosis, and whenever we repeat the bone marrow for any reason, maybe at the time of relapse, for example," explains Dr. Alhejazi. "PET scan we do upon diagnosis, and then upon reassessment."

In Dr. Alahmadi's center, FISH testing is not done in-house but we send it abroad, and it takes up to 2 to 3 weeks to get the results. He says "we prefer to have the results ready by the time of initiation of the therapy since it might have an impact on therapy choice. We try to do FISH cytogenetics with every single bone marrow test with every relapse because sometimes we see new cytogenetics changes with every relapse which reflect a clonal evolution, known in cases of multiple myeloma. With regard to PET-CT, we do not do it routinely but for selected patients, especially in cases of extramedullary myeloma, where it can be used as baseline and follow-up for response assessment." Generally, he says, "we do a low-dose CT scan as the imaging technique for diagnosis and for follow-up."

Dr. Mutahar has found that PET is very useful and very sensitive for cases in which diagnosis is not clear, for example, extramedullary cases, in cases with small volume monoclonal protein, in patients with no measurable disease. "However, it is not for everyone," she says. "For the patients for whom we have a high suspicion of multiple myeloma, we do a low-dose CT."

Dr. Rossi agrees that the anatomical changes on CT is something she and her colleagues are very sensitive to. "Even though the patient will have responded very nicely, the anatomy may not change. You will have the lytic lesions still there. But if you are able to monitor at FDG avidity, that may resolve. We definitely like the PET-CT scan, but I know we are spoiled with our access to it."

MRI in Multiple Myeloma

"The only case for which I would do an MRI is if there is bone plasmacytoma that needs further characterization for orthopedic intervention or radiation, or if I suspect spinal cord compression or vertebral soft tissue," says Dr. Mutahar, "otherwise, we do CT."

Dr. Alahmadi finds MRI useful when he suspects plasmacytoma, but PET and all other test results are negative. "Before I say it is plasmacytoma and I treat with radiation, at minimum I would do MRI of the spine and pelvis looking for bone marrow signal. As it is known based on the IMWG[1,2] criteria, having more than 1 MRI lesion of more than 5 mm would qualify as a diagnosis of myeloma."

Dr. Alhejazi says they sometimes do MRI of the spine in addition to PET scan for patients who complain of back pain to diagnose compression fracture or plasmacytoma especially if there associated radiculopathy, MRI is also used in cases of smoldering myeloma, to make sure the "smolders" are not upgraded. The definition of bone disease in SLiM CRAB is related to MRI finding of bone lesions **(Table)**. A patient with smoldering myeloma will be followed up at least every 3 months in the clinic. Once any of the SLiM CRAB features develop, a patient will be eligible for treatment. I do not treat smoldering myeloma before any of the SLiM CRAB features develop."

S = 60% plasmacytosis
Li = Light chains I/U ratio >100
M = MRI 1 or more focal lesion
C = calcium elevation
R = renal insufficiency
A = anemia
B = bone disease

Table. SLiM CRAB Features
Adapted from Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group Updated Criteria for the Diagnosis of Multiple Myeloma. *Lancet Oncol.* 2014;15(12):e538-e548.

NCCN Guidelines for MM

According to Dr. Rossi, many of her US colleagues, in general, practice current National Comprehensive

Cancer Network (NCCN) Guidelines.[3] However, she wonders whether they are used in other parts of the world. "I have helped write them," she says. "I have never tried to read them. Every time I teach fellows and I bring up the website, it seems more complex than helpful."

Dr. Alhejazi's says his team "does not religiously follow the NCCN Guidelines. There are local guidelines that have been published in different journals, but we follow mostly general guidelines about treating myeloma."

"Honestly, I never follow NCCN Guidelines," admits Dr. Mutahar, "because it's not a guideline per se. It just gives you an approach for the diagnosis and then what treatment to select. Especially, upon relapse, things are more complicated and difficult, it gives only the options of treatment.

A lot of physicians, even hematologists, like it because it is written in a very clear, simplified way. However, it is not one size fits all. You must individualize your approach to each individual patient. You cannot use the same protocols for all patients. It is useful in other malignancies."

Dr. Alahmadi also thinks the NCCN Guidelines are good for other diseases in hematology. "Myeloma is quite diverse. We do not have an A, B, C, D for myeloma. So, there is no first choice. There is no one choice. Basically, you pick and choose your approach based on patient age, comorbidities, functional status, and social status."

Optimal Treatment Sequencing for MM Patients

"When I ask, 'How do you treat myeloma?', the answer is always, 'It depends,'" says Dr. Rossi. "We have so many options, but at least for front line, the list is a little bit shorter. In most places VRd (Velcade [bortezomib], Revlimid [lenalidomide], and dexamethasone) is the standard up front, but most of us in academia have transitioned to using KRd (Kyprolis [carfilzomib], lenalidomide, and dexamethasone)[4] up front," she says.

"The treatment of multiple myeloma is divided based on the features of the patients whether they are transplant eligible or transplant ineligible patients," explains Dr. Alhejazi. "Usually, transplant eligible patients are younger and more fit that can tolerate the transplant. We don't have an age limit for transplant eligibility, but up to 70 years we do consider them for autologous transplant if they don't have significant comorbidities and they are not frail. For transplant eligible patients, our first-line regimen is usually VRd, as a triplet. For the transplant ineligible patients," he says, "many times we start with LEN-Dex, lenalidomide-dexamethasone, and then in many instances where the patient can tolerate the triplet, we add Velcade. Although we have not used it except rarely in myeloma patients up front, we are on the verge of incorporating carfilzomib, to be used as KRd instead of VRd, in the first-line setting for high-risk patients."

In terms of up front, Dr. Alahmadi says until maybe 3 or 4 years ago, they were using VCd (bortezomib, cyclophosphamide, dexamethasone) for both transplant eligible and nontransplant eligible. "We will use a lower dose of Velcade for the elderly patient. Now, we use VRd for all the patients except if they have advanced renal disease," Dr. Alahmadi says. "For some patients, we go with Rd (lenalidomide plus dexamethasone), especially if they are frail and it is difficult for them to come weekly for injection. We try to transplant everyone less than 65 years, selected patients 65 to 70 years. Usually, we do not transplant anyone above 70 years."

"Because both carfilzomib and daratumumab were just approved in Saudi Arabia for relapsed cases," says Dr. Mutahar, "in our minds, we will work to start daratumumab up front in transplant ineligible patients, because it is very well tolerated. I was able to use it up front in an ultra-high-risk young multiple myeloma patient."

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Dr. Alhejazi says they have not used monoclonal antibodies, such as daratumumab, as part of the first-line regimen. "The MAIA trial[5] has tested the addition of daratumumab to lenalidomide and dexamethasone in elderly patients who are transplant ineligible and that has shown definitely a difference. At the moment, we haven't added the monoclonal antibodies to first-line therapy. In the transplant eligible patients, the efficacy of VRd and daratumumab has been tested in the phase 2 GRIFFIN trial,[6] and I am sure the results are going to be in favor of adding daratumumab." He says the results have not yet come out of another phase 3 trial the PERSEUS,[7] which is also evaluating the addition of daratumumab to VRD in transplant eligible patients. "In the future, daratumumab will take its place as part of a combo used in the first-line regimen, whether VRd or KRd this has yet to be answered."

Dosing of Carfilzomib

"In the United States," says Dr.

Rossi, "we have approvals at multiple different dose levels, with multiple partners, different schedules, it makes our community oncologists a little crazy."

"Carfilzomib dosing has been different in multiple trials," says Dr. Alhejazi. Two large trials of carfilzomib use are the ENDEAVOR trial,[8] which used the Kd regimen (carfilzomib, dexamethasone) with 56 mg/m^2 twice weekly, and the ASPIRE trial,[9] which tested KRd use in the second-line setting with 27 mg/m^2 twice weekly. With dosing of carfilzomib, Dr. Alhejazi says that he starts the dose, especially for a patient they are afraid will not tolerate higher doses, at the usual 20 mg/m^2 on the first day of the cycle."

Dr. Mutahar says she has altered her chemotherapy schedule of carfilzomib in response to recent data. "While the twice weekly 27 mg/m^2 dose of carfilzomib was well tolerated, I tried 56 mg/m^2 twice a week with dexamethsone for one patient, and it went well." Dr. Alahmadi says his center does the same as Dr. Mutahar's. "We are using carfilzomib with lenalidomide as the KRd."

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> — Enas Mutahar, MD

Addressing Challenges With Carfilzomib

"The twice weekly scheduling with carfilzomib is a big challenge," says Dr. Alahmadi. "It takes more time compared to bortezomib." He has not seen any patients with renal impairment, but he has had patients with fatigue, cytopenia, and 2 patients who experienced a decrease in ejection fraction on repeated echocardiogram while on carfilzomib," he says, "although there were no symptoms of heart failure." One of these patients Dr. Alahmadi notes had progressed through other lines of therapy. "I did not have anything else to offer other than carfilzomib, so I kept him on Kd and decreased the dose of carfilzomib from 56 mg/m^2 to 36 mg/m^2, per data." When Dr. Alahmadi repeated the ECHO, he says the ejection fraction was back to normal. He explains that because it was not clear what caused the drop, they do an ECHO as a baseline for all patients before starting carfilzomib.

Preexisting Cardiac History

"For patients with a preexisting cardiac problem, if I have other options, I would use them," cautions Dr. Alahmadi. "If I don't, then I would be very cautious with using carfilzomib. I would do serial peripheral neuropathy testing, importantly physical examination to look for any clinical signs of heart failure. I would repeat the ECHO about every 2 or 3 months to see how things are going. And if there are any further changes, I would stop immediately."

Dr. Alhejazi says that the cardiac toxicity and complications with carfilzomib are well known. "Many of the patients who have already had heart failure or fluid overload who are well compensated on treatment can remain on therapy. We titrate the dose and we titrate the amount of fluids given during treatment. In those patients, we try to limit the amount of hydration and IV fluids in order not to induce a decompensation process of heart failure. In patients who do not have any history of heart failure, we use prehydration."

Cytopenia

A recurrent toxicity that Dr. Alhejazi sees is thrombocytopenia or cytopenia. "In general, we have to give some growth factors or withhold 1 or 2 doses, for a week or 2, until patients recover their count and then give them the dose."

Fluid Overload

"The most common problem and challenge that I face is the fluid overload," says Dr. Mutahar. "Some patients reach the stage of pulmonary edema. Of course, when we do the ECHO, we get the answer for why this happened. Most patients who develop fluid overload and pulmonary edema are heavily pretreated."

Dr. Mutahar adds that at her center, they "do an ECHO before treatment, and I do an ECHO routinely every 3 to 6 months based on the patient condition. But if the patient has a cardiac history and I have another alternative, I would choose other than carfilzomib. If the patient does not have an alternative, then I may do a dose reduction with fluid adjustment, the prehydration." On whether to give the fluid the same for all cycles, all patients, or whether to titrate, Dr. Mutahar says that in her chemo pharmacy, "they put it with each individual cycle; cycle 1, 2, 3, and onward. In patients that I am concerned of fluid overload or they have potential to develop overload, then I would just give it in the first cycle."

"I sometimes try that if there are options," says Dr. Rossi. "For patients with renal failure, you may want to maintain the hydration; patients with volume issues, we can take it away very quickly."

When a Patient Relapses

Now that there are so many treatment options for myeloma, once a patient relapses, knowing how to pick what order to go in or which drug for which patient, whether to use a doublet or a triplet or go back to something used before Dr. Alahmadi says depends on multiple factors. "There's no standard regimen

that we use for relapsed patients. It depends on risk profile—previous lines of therapies, response with previous therapies, how they were tolerated, any preexisting comorbidities (preexisting peripheral neuropathy, cardiac or renal issues, cytopenia)—and the social status of the patient, in addition to the risk based on FISH cytogenetics. More importantly, Dr. Alahmadi adds, "when a patient has a relapse, we need to be realistic and think about what available options we have in our hand. Putting that together with the risk profile and social status, we tailor the therapy for our patient. Doublet or triplet? Definitely, I would prefer triplet."

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Dr. Mutahar's approach to relapse patients, either first or second and onward relapses also depends on several factors. "The ones mentioned, social status, and patient preference play major roles," she says "Because we do cover a large area—the distance between our center and where the patient lives is about 4 to 6 hours away in some cases—sometimes we go with orals. Mainly, the first approach to a relapse will depend on the disease and the patient's condition. We discuss with the patient the different options, and then we decide which way to go," says Dr. Mutahar. "Second transplant is always there if the patient has a good response to the first transplant, and he or she is fit and meets the criteria for the second transplant."

Dr. Alhejazi says there are many options to choose from. "Most of the recent trials that have tested a triplet in a relapse-refractory setting in multiple myeloma used either an Rd backbone or a non-Rd backbone. Those which have used an Rd as backbone, unfortunately, are not valid, including ASPIRE and POLLUX,[10] because in these trials only very few patients—only about 12% to 15% of patients—have used lenalidomide as front line, while in reality, now, almost all patients have used lenalidomide as up front. So, the whole combination is not valid for someone who is lenalidomide refractory (LEN-refractory)."

He adds that there are trials that have used proteasome inhibitors, such as the ENDEAVOR using Kd, the CASTOR using DVd,[11] and others like the OPTIMISMM trial,[12] which has combined bortezomib, pomalidomide, and dexamethasone. These combinations are used more now in the second-line setting especially in LEN-refractory patients, although the outcome of non-Rd based trials is inferior to the Rd-based trials."

The main problem in treating relapse is when the patient is refractory to lenalidomide, says Dr. Alhejazi. "In general, in our practice, KRd is the first second-line regimen that we use mostly in those who are not LEN-refractory," he says. "Kd is sometimes used in patients who are frail whom we think cannot tolerate triplet, but we mostly use triplet if we can."

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How to Approach the LEN-Refractory Patient

An important issue in MM management is how to define the LEN-refractory patient when most patients are receiving lenalidomide (LEN) up front in most cases as part of a triplet. Dr. Alhejazi says that lenalidomide is used within a triplet except for patients who are non-transplant eligible who are frail who likely cannot tolerate the triplet, for those patients, "we give them LEN-Dex continuous."

Dr. Alhejazi acknowledges that LEN refractoriness is challenging. "LEN-refractory is not defined the same way everywhere and people tend to define it differently. Patients who are transplant eligible are usually kept on lenalidomide maintenance, which is a smaller dose than the usual lenalidomide that we use in triplet, usually 10 mg daily. Only a fraction of them—perhaps less than 15%—will respond to lenalidomide by increasing the dose to 25 mg," he says. "I think the patient who has been on a lenalidomide-based regimen, the full dose, and progressed either while on the regimen or at least 6 months after the regimen is considered LEN-refractory."

Dr. Mutahar agrees that people define it different ways. "If the patient was not on lenalidomide at the time of relapse and had responded to it in the past, then we could re-challenge with the same immunomodulatory drug, especially if he or she achieved a good response." Dr. Mutahar adds that "sometimes if the patient relapsed while on maintenance therapy, I increase the dose and reassess in 2 cycles. However, not a lot of physicians will do that because the theory is if the patient relapses on LEN, the dose does not matter. However, if you increase the dose, the response will not be the

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best. Sometimes I do it to buy time or to give patients some flexibility."

Dr. Alahmadi notes that it is difficult the patient is relapsing on LEN or he took it within the last 60 days. In practice, we give LEN maintenance for almost all our patients for 2 years—maybe longer if it is well tolerated and they have a high risk. Thus, a good proportion of my patients relapse on LEN maintenance." He says he will increase the dose in patients who are high risk from the beginning—they had a dramatic presentation, bad cytogenetics—and in patients who have some biochemical relapse; he may go up a full dose with the addition of dexamethasone, or even add cyclophosphamide (for example, an RCd). "For the LEN-refractory patient, the idea is you want to buy some time. We know this is a chronic disease, incurable. So, you want to extend your therapy as much as possible, as long as it is feasible" **(Figure 2).**

Switching Class in the LEN-Refractory Patient

"I really like the idea of switching partners," says Dr. Rossi. "I think for physicians who treat other diseases, maybe that sounds like heresy. But in myeloma, you can really sort of recycle drugs and rescue response if you are now switching partners."

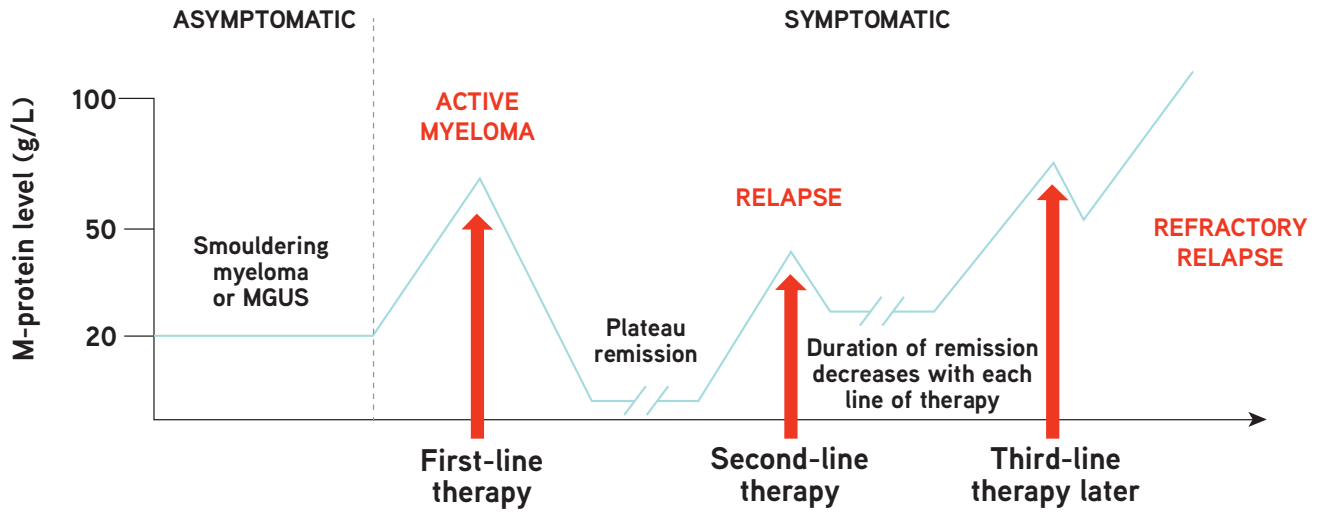
Regarding whether to switch but stay within the same class—to a pomalidomide (Pomalyst) base—or switch to another class, such as carfilzomib or daratumumab, Dr. Mutahar says that she does switch patients who are refracted or not responding. "I do switch them to pomalidomide. And I have a good number of patients who have responded beautifully." Dr. Mutahar provides an example of a patient who did not respond up front. "She was a 36-year-old who presented with diffuse bone lesions, anemia. I induced her with VRd. She achieved stable disease. After that, she started having a little bit of biochemical progression. So, it is the same class. Someone could argue that it is better to switch class rather than agents."

Dr. Rossi thinks this is an argument that comes from other disciplines, that is to switch class of drug if the patient is progressing. "However, we have data for pomalidomide in LEN refractory and carfilzomib in bortezomib refractory, making the argument that moving to another agent of the same class makes sense." In myeloma, she says, "upon progression, the physician has the option to switch to a new drug, be it a new member of same class or a new class altogether."

"Pomalidomide is a choice in patients who have been labeled as LEN-refractory," says Dr. Alhejazi, "although fewer trials have tested the combinations using pomalidomide than those testing lenalidomide. However, I usually try to switch classes to something else."

Of the options, Dr. Alhejazi says,

Despite therapeutic progress, multiple myeloma remains incurable and the majority of patients relapse



Adapted from 1. Durie B. Concise Review of the Disease and Treatment Options. International Myeloma Foundation. 2017 edition; 2. Kumar SK, et al. Mayo Clin Proc 2004;79:867-74

MGUS, monoclonal gammopathy of undetermined significance

Figure 2. Natural history of multiple myeloma.

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"Pom-dex (pomalidomide-dexamethasone) is a very weak regimen but pom-cyclo-dex is a better regimen that can give you a PFS around 11 months probably. In the OPTIMISMM trial that has used bortezomib (Velcade), pomalidomide, and dexamethasone (VPd), the limitation in these regimens is that the patient has to be nonrefractory to bortezomib. Some patients who are high risk will be kept on bortezomib maintenance. And then when they progress, Velcade-based regimens are not a good choice in those patients."

Future Perspectives in MM Treatment

"The chimeric antigen receptor (CAR) T cell therapy or the BiTE (bispecific T-cell engager) therapy, may be the future for myeloma," says Dr. Alahmadi. "However, the problem so far is that—if we look at all the clinical trials evaluating the CAR T cells or the new BiTE, which were presented at the ASH Meeting—the treatment is used in later stages of the disease, when the T cells become more dysfunctional. I think that is part of the reason why it works in the beginning, but then most of the time the response is not durable." He suggests that "maybe we need to change the sequence a little bit."

"The CAR T cells and BiTEs are promising modalities of treatment," says Dr. Alhejazi. "Currently, we think of CAR T cells as last resort in treating multiple myeloma. Although there is a very good response in the beginning, the problem with most of the initial anti-BCMA (B cell maturation antigen) CAR T cells is that the remission does not last for long. Now, BiTEs, I guess are promising from the previous experience with ALL. I think they are going to work well hopefully. So, we will wait for them to come into the market." On what his thoughts are for the future of MM treatment, Dr. Alhejazi expects "we will find a combination of these new drugs that will probably cure some patients of multiple myeloma with the up-front therapy using all these strong novel agents from the beginning."

Dr. Rossi notes that "we also have some allogeneic CAR T therapies, where we do not depend on the patient's T cell repertoire. Again, it is very promising, but we have a long way to go."

Minimal Residual Disease

Minimal residual disease (MRD) is a somewhat recent topic in the evaluation of myeloma (see **Figure 3** for the IMWG consensus criteria for response and MRD assessment in MM). However, it is currently not in use in Saudi Arabia. Dr. Mutahar says she has access to flow cytometry, but it is not valided. "I have needed MRD assessment in a few patients who were in CR post-transplant and I needed to

Stable Disease	Progressive Disease	Clinical Relapse	Relapse from CR	Relapse from MRD negative
Not meeting criteria for: • Complete response (CR) • Very good partial response • Partial response • Minimal response • Progressive disease	25% from lowest confirmed response value in ≥1 of the following: • Serum M-protein (↑≥0.5 g/dL) • Serum M-protein ↑ ≥1g/dL, if lowest M component ≥5 g/dL • Urine M-protein (↑≥200 mg/24 h) • Without serum + urine M-protein, difference between involved + uninvolved FLC (↑>10 mg/dL) • Without serum + urine M-protein and without involved FLC, bone marrow plasma-cell percentage irrespective of BL status (↑≥10%) • New lesion(s), ≥50% ↑ from nadir in SPD of >1 lesion, or ≥50% ↑ in longest diameter of previous lesion >1 cm • ≥50% ↑ in circulating plasma cells (min 200 cells/μL) if only measure of disease	≥1 of the following: • Direct indicators of ↑ disease and/or end organ dysfunction (CRAB features) related to underlying clonal plasma cell proliferative disorder • New soft tissue plasmacytomas or bone lesions • Definite ↑ in size of existing plasmacytomas or bone lesions (defined as 50% ↑ (and ≥1 cm) as measured serially by the SPD of measurable lesion • Hypercalcemia (>11 mg/dL) • ↓ in hemoglobin of ≥2 g/dL not associated with Tx or other non-myeloma-related conditions • ↑ in serum creatinine ≥2 mg/dL from the start of therapy and attributable to myeloma • Hyperviscosity related to serum paraprotein	≥1 of the following: • Reappearance of serum or urine M-protein by immunofixation or electrophoresis • ≥5% plasma cells in the bone marrow • Any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcemia)	≥1 of the following: • Loss of MRD negative state (evidence of clonal plasma cells on NGF or NGS, or positive imaging study for recurrence of myeloma) • Reappearnace of serum or urine M-protein by immunofixation or electrophoresis • ≥5% clonal plasma cells in bone marrow • Any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcemia)

FLS, free light chain; NGF= next-generation flow; NGS = next-generation sequencing; SPD = sum of the products of the maximal perpendicular diameters.

Figure 3. Simplified Response Criteria for Multiple Myeloma

(Adapted from Kumar SK, et al. NCCN Clinical Practice Guidelines in Oncology: Multiple Myeloma, Version 3.2020. March 10, 2020; Kumar S, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *Lancet Oncol.* 2016;17(8):e328-e346.)

know the depth of their CR, but unfortunately, it is not validated."

Dr. Alahmadi thinks next generation sequencing might be useful. "Also, the PET-CT gives you an idea about the MRD status. If the patient has, for example, a negative PET. I use this for a few patients, especially when they have lots of extramedullary disease, and it gives me an idea about how deep of a response they have achieved."

Currently, Dr. Alhejazi's center does the stringent CR based on the mutual tests and serum free light chain, but it does not do MRD in multiple myeloma.

"We know for a fact those patients who achieve MRD negatively have better prognosis and increased PFS and probably overall survival. But until now, there are no mature trials that treat according to MRD testing either in the second line or subsequently, he says. "In the future, MRD testing, in addition to being prognostic is going to direct therapy after a certain induction regimen or after transplant, in deciding whether patients need to be given maintenance, and for how long, or who needs consolidation. I guess post-consolidation maintenance also is going to be MRD driven, but that is too early to say."

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