Updates on the Rapidly Changing Therapeutic Landscape in Multiple Myeloma

Source: Adapting Clinical Practice to a Rapidly Changing Therapeutic Landscape in Multiple Myeloma


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As we continue to understand more about the biology of multiple myeloma (MM) and the number of treatment options for patients with MM continues to expand, keeping track of the current standard of care practices and emerging new treatment strategies has become even more challenging. In this commentary, we will summarize our thoughts on how we are managing patients with MM in clinical practice.

Smoldering Myeloma

Jesús F. San-Miguel, MD, PhD

The first step in patient care is diagnosis and staging of MM. Deciding whether a patient has smoldering vs active MM can be a challenge. Clearly, we agree that if a patient has symptomatic, MM-defining events using the CRAB criteria (calcium elevation, renal dysfunction, anemia, and bone disease), we would treat this disease as newly diagnosed, active MM. However, some patients do not have traditional MM-defining events but do have biochemical features that also result in a diagnosis of active MM using the SLiM-CRAB criteria (≥60% clonal bone marrow plasma cells, serum free light chain ratio [FLC] ≥100 for involved κ or ≤0.01 for involved λ, or MRI with >1 focal lesion >5 mm in size).

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Patients who do not have active MM but do have ≥10% plasma cells or M protein of ≥3 g/dL are considered to have smoldering disease, and these patients should be risk stratified as either high, intermediate, or low risk. High-risk smoldering MM is defined as having a median time to progression of ≤2 years, which is approximately 1 in every 3 patients with smoldering MM.

The International Myeloma Working Group proposed a risk classification called the 2/20/20 model, which includes 3 characteristics to determine risk: the presence of M component of >2 g/dL, FLC ratio of >20, and >20% bone marrow plasma cells. If a patient has 2 or 3 of these risk factors, the 2-year risk of progression is 46%, and these patients are considered to have high-risk smoldering MM. However, a patient's individual risk of progression can be very different with 20% bone marrow plasma cells vs 40% or 50% bone marrow plasma cells or if the FLC ratio is 20 vs 40 or 50. Therefore, a more precise and individualized score tool was subsequently developed to classify individuals by their actual risk of progression. The MyeRisk calculator assigns a total risk score based on the FLC ratio, level of M protein, percent of bone marrow plasma cells, and cytogenetic abnormalities.

Other risk factors also can help identify a higher risk of progression at 2 years, including an evolving pattern of disease, such as an increasing M component or decreasing hemoglobin level, those with double-hit or triplet-hit cytogenetics, the presence of a new or increase in an existing focal lesion or progressive diffuse infiltration on bone MRI or PET positivity without lysis, and the presence of >0.02% circulating plasma cells. In these situations, patients will likely progress to active MM quickly, and therapeutic intervention should be considered.

The phase III QuiRedex and E3A06 and trials both have shown that lenalidomide plus dexamethasone (Rd) or lenalidomide alone can reduce the risk of end-organ damage and delay disease progression in patients with high-risk smoldering MM. Moreover, in the QuiRedex trial an overall survival benefit has been also observed. Single-agent therapy with anti-CD38 monoclonal antibodies are being explored in this setting, with promising early results. Several additional phase II clinical trials are exploring combination approaches for this patient population, including with elotuzumab plus Rd, ixazomib plus Rd, and carfilzomib plus Rd (KRd) for 8 cycles followed by lenalidomide maintenance. The results of these trials are promising, but the number of patients is small, and the follow-up is short.

Finally, some trials are using more aggressive treatment approaches for patients with high-risk smoldering MM, with the hope of potentially reaching a cure for this disease. The phase II GEM-CESAR trial includes KRd induction therapy for 6 cycles followed by autologous stem cell transplant (ASCT), consolidation with 2 more cycles of KRd, and lenalidomide

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Poll

Which of the following topics related to the care of patients with MM do you want to learn more about?

- **A.** When to initiate therapy
- **B.** Managing older patients
- **C.** Use of novel agents in R/R

maintenance for 2 years. The phase II ASCENT trial is using a quadruple combination of daratumumab plus KRd for 12 cycles without ASCT followed by daratumumab plus lenalidomide maintenance for 12 cycles.

Until we have more data from these ongoing trials, for those patients who want to start treatment, a clinical trial is ideal, and therapy similar to what we use in active MM according to a patient's age and fitness would be reasonable, based on the positive data reported for Rd. For those who do not wish to start treatment for high-risk smoldering MM, ongoing monitoring for an accumulation of risk factors is essential, and therapy should be initiated immediately when a patient progresses to active disease or shows evolving biomarkers associated with active disease.

Frontline Therapy for Active MM

Philippe Moreau, MD
For patients who are diagnosed with active MM who are eligible for ASCT, important issues to discuss include the use of triplet vs quadruplet therapy for induction, the use of upfront vs delayed ASCT, whether we need more aggressive strategies for high-risk disease, and using lenalidomide single agent or 2 agents for maintenance therapy.

Based on the European Hematology Association and European Society for Medical Oncology guidelines, options for induction therapy are either bortezomib plus Rd (VRd) or bortezomib/thalidomide/dexamethasone (VTd) plus daratumumab, a quadruplet, followed by a single stem cell transplant and lenalidomide maintenance. The mSMART guidelines further stratify patients by risk: for standard-risk disease, VRd induction followed by ASCT and lenalidomide maintenance is preferred, but not systematically proposed. For high-risk disease, quadruplet induction with daratumumab plus VRd can be considered, along with consideration for tandem ASCT and bortezomib-based maintenance.

For patients who are transplant candidates, we generally recommend VRd or daratumumab-based quadruplet therapy (daratumumab plus VTd or daratumumab plus VRd, based on the CASSIOPEIA trial and the GRIFFIN trial, respectively). In Europe, daratumumab plus VRd is not yet approved, and VRd is not officially approved by the European Medicines Agency prior to ASCT, but some centers already are using these approaches in anticipation of regulatory approval. For instances where these regimens are not available, bortezomib/cyclophosphamide/dexamethasone or VTd also can be considered.

After induction, ASCT and lenalidomide maintenance is recommended for standard-risk disease, but lenalidomide plus a proteasome inhibitor (PI) is recommended for high-risk disease. In Europe, we also may consider a tandem ASCT for high-risk disease (based on the EMN02 trial), although this may not be needed along with quadruplet induction therapy. Currently,

- **D.** Emerging investigational agents and strategies
- **E.** Managing disease and treatment-related adverse events

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delayed ASCT is not recommended outside of clinical trials in most countries, and we are recommending upfront ACST to our patients. If a patient requests delaying ASCT and your facilities allow that, stem cells should be collected before an additional 4 cycles of VRd, and ASCT can be performed at first relapse.

For patients who are diagnosed with active MM who are not eligible for ASCT, important issues to discuss include whether to use combinations with CD38 as first-line therapy, how to incorporate frailty scoring systematically, how to manage adverse events in this older patient population with comorbidities, and should we use a fixed duration of treatment or continue treatment until progression.

For nontransplant candidates, there are 2 recommended options: daratumumab plus Rd (DaraRd) or VRd (based on the MAIA and SWOG777 trials, respectively) followed by lenalidomide maintenance. Additional options, particularly in Europe, include daratumumab plus bortezomib/melphalan/prednisone or Rd. The mSMART guidelines recommend lenalidomide maintenance for standard-risk disease or bortezomib maintenance for high-risk disease after either VRd or DaraRD in this setting.

In terms of toxicity, VRd has a higher rate of infection and peripheral neuropathy compared with Rd. When looking at a frailty subgroup analysis of DaraRd in the MAIA trial, there was a clinical benefit of DaraRd regardless of the frailty status; however, for frail patients, the treatment discontinuation rate was higher, as was the death rate. There also was a higher rate of neutropenia with the addition of daratumumab, translating into a higher rate of grade 3/4 pneumonia with DaraRd vs Rd alone.

Treatment After First Relapse

S. Vincent Rajkumar, MD:
At time of first relapse, if the patient is still sensitive to lenalidomide, several lenalidomide-based regimens could be considered, including DaraRd or KRd if the patient is daratumumab refractory. For patients who are refractory to lenalidomide, an anti-CD38 combination regimen without lenalidomide is preferred. These include carfilzomib/dexamethasone with either daratumumab or isatuximab or pomalidomide/dexamethasone with either daratumumab or isatuximab. For patients who are refractory to both lenalidomide and daratumumab, pomalidomide/bortezomib/dexamethasone, pomalidomide/carfilzomib/dexamethasone, or pomalidomide/elotuzumab/dexamethasone can be considered.

Therapy selection for relapsed MM is more complicated than for newly diagnosed MM, because it depends on when is the relapse occurring, what the previous therapy was and if they were still receiving therapy at the time

of the relapse, how the patient responded to previous therapy, how aggressive the relapse is (eg, biochemical relapse only vs symptomatic relapse), and what kind of treatments the patient can tolerate (performance status, comorbidities, adverse events [AEs] with previous therapy). My acronym for these considerations is TRAP (timing of the relapse, response to prior therapy, aggressiveness of the relapse, performance status).

Unfortunately, we do not have any trials comparing a triplet with a triplet regimen to decide which should be preferred. So, what is important to remember is that using any of these triplet regimens is an option as long as they are recommended in a logical fashion to ensure that the different classes of agents are used sequentially with ≥2 new drugs in each subsequent line of therapy. If you are changing the regimen, dexamethasone remains the same, so you change the other 2 drugs so that you give the patient the best option of responding.

Treating Relapsed/Refractory (R/R) MM After Multiple Lines of Therapy

Thomas G. Martin, MD:
For patients who have experienced disease relapse after receiving our standard agents, we now have some newer options for RR MM, including those targeting BCMA. Currently approved BCMA-targeted therapeutics include belantamab mafodotin (an antibody–drug conjugate) and 2 CAR T-cell therapies, idecabtagene vicleucel and ciltacabtagene autoleucel. Belantamab mafodotin is currently approved for patients who have received ≥4 previous therapies, including an anti-CD38 monoclonal antibody, a PI, and an immunomodulatory drug (IMiD), based on the DREAMM trial. The CAR T-cell therapies are approved for patients who have received ≥4 previous lines of therapy, including an IMiD, a PI, and an anti-CD38 monoclonal antibody, based on the KarMMa and CARTITUDE-1 trials.

Currently, there is not universal access to these BCMA-targeted agents for various reasons. Ocular toxicity associated with belantamab mafodotin necessitates the requirement of a Risk Evaluation and Mitigation Strategy program and good collaboration with an ophthalmology colleague. Belantamab mafodotin is accessible, however, as an “off-the-shelf” treatment and is a great option for many patients. For the CAR T-cell therapies, widespread use has been hampered by the limited number of manufacturing slots, inadequate vector supply, as well as a need to administer these therapies at a certified facility. CAR T-cell therapy is also associated with cytokine-release syndrome and neurotoxicity, thus necessitating patient fitness. But AEs associated with CAR T-cell therapy is manageable, particularly as we optimize treatment strategies and learn more about how to control them.

Regardless of the type of BCMA-targeted therapy selected, the response rates are impressive, even in a heavily pretreated patient population. In addition to the approved BCMA-targeting agents, we also have initial phase I

data on the use of anti-BCMA bispecific antibodies or bispecific T-cell engagers for R/R MM. The single-agent response rates with these agents also are encouraging, and responses appear to deepen over time, although follow-up is limited and duration of response has not been reported. Overall, for a fit patient with R/R MM after multiple lines of therapy, I would recommend proceeding to a BCMA CAR T-cell therapy if possible. In less fit patients, I would recommend belantamab mafodotin (or a bispecific antibody once they are approved). Clinical trials investigating novel agents for R/R MM would also be appropriate.

Brian G.M. Durie, MD:
BCMA-targeted therapy is a great option for patients after multiple relapses. After multiple lines of therapy, there also are additional options for our patients to consider, including the XPO inhibitor selinexor and the BCL2 inhibitor venetoclax for patients with t(11;14), as well as more traditional agents such as alkylator-based therapy, cyclophosphamide, and melphalan.

Initially, the phase II STORM trial led to approval of selinexor plus dexamethasone in patients with R/R MM after ≥4 previous therapies, including ≥2 PIs, 2 IMiDs, and an anti-CD38 monoclonal antibody. The phase III BOSTON trial evaluated the combination of bortezomib/dexamethasone vs selinexor/bortezomib/dexamethasone and led to the approval of selinexor/bortezomib/dexamethasone for patients with MM who have received ≥1 previous therapy. Common AEs associated with selinexor include hematologic AEs and gastrointestinal AEs such as nausea, decreased appetite, diarrhea, and vomiting. In the BOSTON trial, selinexor was administered once weekly, which was found to be better tolerated compared with twice-weekly dosing in the STORM trial. There also are some data with selinexor in combination with carfilzomib and even daratumumab that suggest these combinations may be effective for patients with heavily pretreated R/R MM.

For a patient with t(11;14) translocation, venetoclax can be considered during the course of their disease. Venetoclax has been studied as a monotherapy and in combination with dexamethasone and various other combinations including with daratumumab/dexamethasone. When considering venetoclax for patients with R/R MM, it is important to remember the cautionary tale with the BELLINI trial, which compared venetoclax/bortezomib/dexamethasone with bortezomib/dexamethasone. In this trial, there was a progression-free survival (PFS) benefit with the venetoclax combination in the overall patient population, but this did not translate into an overall survival (OS) benefit. In fact, in an unselect population, OS was worse with the addition of venetoclax due to more deaths associated with infection and cardiac complications. However, patients with t(11;14) or high BCL2 expression have significantly better PFS with a trend toward improved OS.

Finally, some of our more traditional MM therapies also can be an option in heavily pretreated patients. Cyclophosphamide/dexamethasone is an inexpensive oral regimen that can be effective in delaying disease progression and has quite manageable AEs. In the current era, very few patients are alkylator refractory in advanced disease, so alkylator-based therapy is something to consider. Melphalan also is something I may consider for some patients with penta-refractory R/R MM. At a dose of 25 to 40 mg/m^2 every 6 weeks for 2-3 doses, melphalan can be effective and potentially better than cyclophosphamide-based regimens.

Your Thoughts?
How is your care of patients MM changing as new agents are approved? Answer the polling question and join the conversation by posting a comment in the discussion section.

Discussion

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