Selecting Treatment for Relapsed/Refractory Multiple Myeloma in the Era of Multiple Choices

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Keeping up with the many treatment advances in relapsed or refractory multiple myeloma can be a challenge for even the most informed providers, according to Jorge J. Castillo, MD, Clinical Director, Bing Center for Waldenström’s Macroglobulinemia, Dana-Farber Cancer Institute, Boston, MA.

“In myeloma, a higher variety of medications have been approved in recent years than in any other oncology malignancy,” Dr Castillo said at the NCCN 2019 Hematologic Malignancies meeting. “And that, in itself, is a good thing. But then it also gives us a number of headaches.”

The main headache, he says, is simply deciding which treatment options to use for which patient. The NCCN guidelines for multiple myeloma list 8 preferred regimens alone, in addition to more than 20 recommended regimens. Choice of treatment comes down to personalization, according to Dr Castillo.

Treatment Selection

Disease-related factors. Deciding on a course of treatment for relapsed or refractory multiple myeloma often seems less scientific and more of a “wheel of fortune,” he said. To hone this process, first consider an individual’s disease-related factors, such as the nature of relapse (indolent vs aggressive), risk stratification (high, intermediate, or low), genomic abnormalities, and disease burden.

Patient-related factors should also be carefully weighed, especially patient preferences (intravenous vs oral therapy, distance to treatment center) and clinical considerations, such as renal insufficiency. Almost 50% of all patients with multiple myeloma will have some degree of renal insufficiency; in these patients, providers should favor cyclophosphamide, proteasome inhibitors, and dose-reduced immunomodulatory drugs (IMiDs), because these are more likely to be effective, but with lower toxicity than other drugs.

“In the relapsed and refractory setting, patient preference has become much more important,” Dr Castillo noted.

Previous therapy is also a critical factor that should inform treatment decisions. Consider whether the patient progressed while receiving proteasome inhibitors or IMiDs, and if they progressed on or off maintenance. What was the depth and duration of their response?

Treatment toxicity and patient comorbidities should also be considered. Speaking in general terms, Dr Castillo warns clinicians to be wary of using bortezomib and thalidomide in patients with preexisting neuropathy, carfilzomib in patients with cardiac issues and in elderly patients, daratumumab in patients with pulmonary issues, and IMiDs in those with thrombotic episodes.

Although these drugs are not contraindicated, knowing which treatments may result in worse outcomes in certain populations can help to narrow down the options.

“Every intervention that we have will be related to some toxicity,” he said. “So, we need to make sure that the benefit we provide to our patients is higher than the potential toxicity.”

Triplet Therapy After Relapse

Combination treatment with lenalidomide and dexamethasone has extended survival and time to progression in relapsed or refractory multiple myeloma. However, “triplets are the way to go, not only for frontline disease, but also for relapsed disease,” Dr Castillo says.

Many studies have explored triplet therapy in patients with relapsed or refractory disease who had minimal (≤20%) previous exposure to lenalidomide. In these studies, adding carfilzomib to a lenalidomide-dexamethasone regimen showed promising efficacy after first relapse, as did adding the oral proteasome inhibitor ixazomib to the lenalidomide-dexamethasone regimen in the relapsed or refractory setting.

Daratumumab added to a lenalidomide-dexamethasone regimen has demonstrated significant improvements in progression-free survival (PFS), and elotuzumab, when added to the combination therapy in patients with minimal lenalidomide exposure, has also shown promising efficacy.

However, Dr Castillo warned that the applicability of these findings is limited, because many patients in clinical practice will have had higher exposure to lenalidomide. In patients with previous lenalidomide exposure, adding carfilzomib to dexamethasone led to a “remarkable” PFS benefit versus the combination of bortezomib-dexamethasone. In addition, evidence has shown that adding daratumumab to bortezomib-dexamethasone was superior to bortezomib-dexamethasone alone.

Dr Castillo added that certain toxicity trends should also serve to guide treatment. For example, neuropathy...
is often more common in patients using proteasome inhibitors; infections are more common with daratumumab combinations, and cardiotoxicity is more prominent with carfilzomib therapy. Certain side effects, such as diarrhea, occur across the board.

For patients in second relapse or later, “pomalidomide-based regimens are an important resource,” but providers should remain vigilant about the risk of neuropathy, Dr Castillo advises.

Primary Refractory Disease

Clinical trials have yet to be designed solely for patients with primary refractory disease. “We don’t have clinical data supporting specific approaches in this type of patient, besides getting them to transplant early and using a triplet or even a quadruplet as data accumulate,” Dr Castillo said. He listed recommendations to guide the treatment of these patients:

1. First, autologous stem-cell transplant (ASCT) should be standard in transplant-eligible patients with relapsed disease after primary therapy that did not include ASCT.
2. A second ASCT should be considered for patients relapsing after primary therapy that included ASCT with initial remission after 18 months.
3. Finally, allogeneic stem-cell transplantation should be considered in patients with high-risk disease and early (<24 months) disease relapse after primary therapy that included ASCT.

General Rules of Thumb

Dr Castillo also listed a few general rules of thumb:

1. Consider nonlenalidomide triplets in patients whose disease progressed during lenalidomide maintenance, but a lenalidomide-based triplet is advised in those patients who had a prolonged PFS after lenalidomide-based induction.
2. Consider a triplet with different novel agents in patients with primary refractory disease.
3. Always consider referring for transplant if no ASCT was performed during induction.

According to Dr Castillo, current research in multiple myeloma is focusing on CAR (chimeric antigen receptor) T-cell therapies, antibody-drug conjugates, and bispecific T-cell engagers, and these emerging treatments should be on all providers’ radar.

Biosimilars Are Key Components of Oncology Today: Brush Up on the Basics

A n increasing number of biosimilars have been approved in the United States, but many clinicians are still poorly informed about what constitutes a biosimilar, and what is involved in their unique pathway to approval, said Andrew D. Zelenetz, MD, PhD, Medical Oncologist, Division of Hematologic Malignancies, Memorial Sloan Kettering Cancer Center, New York City. He discussed this topic at the NCCN 2019 Hematologic Malignancies meeting.

Biologics are complex, but key, components of modern medicine, particularly in oncology, but the biosimilar pathway establishes a safe and effective means of proving biosimilarity while ensuring competition among biologic drugs.

“If we’re going to make room for new innovations, we have to pay a little bit less [for these drugs] than we have been for the last 20 years,” Dr Zelenetz said.

The list of FDA-approved biosimilars continues to grow in oncology and supportive care, and oncology providers should be informed about these important drugs.

What Is a Biosimilar?

Biosimilars are drugs that have been shown to be highly similar to a reference (or innovator) biologic agent, based on appropriate nonclinical and clinical studies.

“The biosimilar pathway is an abbreviated pathway for things that are truly biosimilar,” Dr Zelenetz explained.

There are tight regulations about how much a molecule can “drift,” but it is important to understand that biologic molecules are always biosimilars of themselves. Biosimilars undergo exhaustive physiochemical, functional, and immunogenicity assessments to establish “fingerprintlike similarity” to the reference drug. “Even the impurities have to be the same,” he added. “I know that sounds weird, but it’s true.”

Most important, the clinical efficacy and safety of the biologic molecule must have been demonstrated by the reference drug (ie, the innovator drug), and the biosimilar must not be different from the innovator drug in a clinically meaningful way.

“So it’s not that the biosimilar has to recreate the
wheel,” Dr Zelenetz said. “If you had to recreate the wheel, there would be no advantage and no reason to make a biosimilar.”

For example, he said, duplicating every single clinical trial done with rituximab between 1997 and today would never be cost-effective. So when a biosimilar is approved by the FDA, there should not be an expectation that there will be differences in safety and efficacy compared with the reference agent.

The Role of Extrapolation in Biosimilar Development

Extrapolation—the expansion of use to other approved indications based on clinical and safety data from 1 indication—is a key concept in the development of biosimilars. This process, which can provide substantial savings in drug development, requires that biosimilars meet certain criteria so that the mechanism of action of the drug, the pharmacokinetics, the pharmacodynamics, and the immunogenicity must all be the same from one indication to another.

“So if you have a biologic that meets these requirements, you should be able to extrapolate from one indication to another,” Dr Zelenetz said.

For example, data from a clinical trial of trastuzumab (a HER2/neu receptor antagonist) in the setting of HER2-overexpressing metastatic breast cancer could reasonably be applied to the adjuvant setting, or even to the treatment of HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma, because the mechanism of action, pharmacokinetics, pharmacodynamics, and immunogenicity do not differ between indications.

However, although a clinical trial of rituximab versus biosimilar rituximab in rheumatoid arthritis demonstrated virtually identical results, leading to the FDA’s approval of the biosimilar candidate for that indication, these data could not reasonably be extrapolated to the lymphoma setting.

A study of the biosimilar rituximab-abbs versus its reference rituximab would have to be carried out in the lymphoma setting to obtain biosimilar approval for that indication.

“The study needs to be in a suitably sensitive population, and in my opinion, the most sensitive indication would be single-agent rituximab in untreated follicular lymphoma,” he said. “Several of the biosimilars have used that exact study design, because it is in fact highly sensitive.” Based on highly similar outcomes from the study comparing the 2 agents, rituximab-abbs was also approved by the FDA (in November 2018) for patients with untreated, advanced-stage follicular lymphoma.

This biosimilar approval was restricted to this specific indication, but Dr Zelenetz argues that rituximab-abbs should be extrapolated to the treatment of other types of lymphoma.

“Even though the approval was restricted, there are no data suggesting that they shouldn’t have gotten full extrapolation. I suspect it was because the sample size of the study was relatively limited, and the FDA was being conservative,” he suggested.

Extrapolation should only be considered for indications where the mechanism of action is identical to that studied in the pivotal trial. In the absence of sound justification for extrapolation, additional clinical trials are necessary.

According to Dr Zelenetz, clinicians generally want certain findings established before they are comfortable with extrapolation, including similar clinical efficacy and time-to-event end points.

“And we’d like to see truly sensitive indications be tested for the evaluation of these drugs, so we know that the effect is really related to the drug that we’re studying,” he said.

Interchangeability

It is also important to realize that the standards for “interchangeability” are different and more stringent than for biosimilarity. The safety standards for determining interchangeability between biosimilars and reference drugs require that the biosimilar produces the same clinical result as the reference in any given patient, and the risk of safety or diminished efficacy because of alternating or switching between the biosimilar and the reference product is no more than using the reference drug without switching.

“No drug yet has been approved as interchangeable,” Dr Zelenetz said. “It is a higher standard than biosimilarity.”

What’s in a Name?

When first deciding what to name biosimilars, some argued that using the same name for an innovator drug and its biosimilar would make it too difficult to trace any rare adverse events that arise, although it would communicate that these agents are “highly similar.” Using different names would clearly distinguish the biosimilar from the reference drug, but this may cause confusion about whether the agents are “highly similar,” and could impede adoption and substitution.

The FDA’s solution was to use the originator name, followed by a suffix containing 4 random letters, such as rituximab-abbs or filgrastim-aafi, a biosimilar to Neupogen approved in June 2018. Currently, all biologic drugs, including all innovator molecules, are assigned these 4-letter suffixes. For example, although rituximab is the innovator drug, if it were developed and approved today for the first time, it would have carried a random 4-letter suffix after its name.
What Is the Role of Chemoimmunotherapy in the First-Line Treatment of Chronic Lymphocytic Leukemia?

We are in a “golden age” in chronic lymphocytic leukemia (CLL), according to Andrew D. Zelenetz, MD, PhD, Medical Oncologist, Division of Hematologic Malignancies, Memorial Sloan Kettering Cancer Center, New York City.

“We’ve made enormous progress in the treatment and management of the disease with multiple new agents, and we’ve seen a lot of data over the last few years about exciting new small-molecule inhibitors. But this has raised an important question—What is the role of chemoimmunotherapy in the management of CLL?” he asked at the NCCN 2019 Hematologic Malignancies meeting.

To address this question, Dr Zelenetz moderated a debate between 2 investigators who have played key roles in the study of chemoimmunotherapy and small-molecule inhibitors.

William G. Wierda, MD, PhD, Section Chief, Chronic Lymphocytic Leukemia, M.D. Anderson Cancer Center, Houston, TX, argued in favor of small-molecule inhibitors, whereas Jennifer R. Brown, MD, PhD, MS, Director, Chronic Lymphocytic Leukemia Center, Dana-Farber Cancer Institute, Boston, MA, supported the role of chemoimmunotherapy in CLL.

Con: There Is No Role for Chemoimmunotherapy in CLL

“We’re in a new era,” said Dr Wierda. “We have more effective treatments than we have ever had. And I would argue that these days, there really isn’t a role for chemoimmunotherapy in the front line or in relapsed therapy.”

According to Dr Wierda, the goals of therapy are “shifting and evolving,” in the management of patients with CLL.

“The other key point to remember is that if these patients fail chemoimmunotherapy, they can go onto a small-molecule inhibitor–based therapy, which is associated with a very long survival,” he added. “We may not ever see an overall survival difference in these trials, because patients will cross over to the alternative treatment.”

If chemoimmunotherapy is being considered, Dr Wierda supports the use of the FCR (fludarabine, cyclophosphamide, and rituximab [Rituxan]) regimen over bendamustine (Bendeka) plus rituximab. Data show a plateau on the survival curve for patients treated with FCR who have a mutated IGHV, which is not appreciated with bendamustine-based treatment, he said.

Dr Wierda and his colleagues have recently been testing the efficacy of combination treatment with ibritinib and venetoclax (Venclexta) in a phase 2 trial, and have seen “very, very high MRD [minimal residual disease]-negative rates, about 70% in patients who have had combined therapy for 18 months,” he said.
Pro: There Is a Role for Chemoimmunotherapy in CLL

Dr Brown argues that despite all these new agents and recent studies, there remains a role for chemoimmunotherapy in the treatment of CLL.

She said that although treatment with ibrutinib or with venetoclax plus obinutuzumab (Gazyva) did improve PFS in the studies discussed by Dr Wierda, these treatments did not affect overall survival, meaning patients are not living longer on these drugs.

“Admittedly, RESONATE-2, which compared ibrutinib and chlorambucil, did report an overall survival benefit, but this was due to the very poor comparator of chlorambucil, and very limited crossover,” Dr Brown said. But as seen in the iLUMINATE and Alliance trials, the overall survival curves completely overlap.

Although ECOG E1912 did report an overall survival benefit with ibrutinib plus rituximab, she said that this was “based on extremely few events, many of which were not clearly related to the disease or its treatment.” She added that these data are “not believable,” and will need to be further evaluated with longer follow-up.

In fact, she added, PFS is not even improved for the 50% of patients with low-risk disease, and those patients can have prolonged treatment-free remission with chemoimmunotherapy—or even cure—if they are candidates for the FCR regimen.

The low-risk subgroup of patients with IGHV mutation did equally well with chemoimmunotherapy as with targeted agents in the ECOG and in the Alliance trials, at least with current follow-up, she pointed out. Even in the CLL14 trial, the subgroup with IGHV mutation did as well with chlorambucil plus obinutuzumab (chemoimmunotherapy) as with venetoclax plus obinutuzumab (combined immunotherapy).

“In no other disease do we give up potentially curative therapy for the requirement of continuous therapy with ongoing residual disease, cumulative side effects, and clearly no cure, which is what we’re talking about with ibrutinib,” she said. “Even if, eventually, ibrutinib did have similar PFS, it would still have the requirement of continuous therapy, toxicity, and cost.”

In terms of side effects with ibrutinib and venetoclax, they are “mixed and distinct from chemoimmunotherapy, but not necessarily better,” she said; they are associated with significant cardiac, infectious, musculoskeletal, and skin adverse events seen over time.

Financial toxicity is another significant issue with these drugs, Dr Brown noted. An estimate of the cost impact of moving oral targeted therapy, such as ibrutinib, from the relapsed setting to the front line is associated with a 6-fold increase in cost.

“And this is not all to the healthcare system. It’s also out of pocket to the patient, with estimates of about $60,000 out-of-pocket costs for Medicare patients receiving front-line ibrutinib,” she said. “We know that most patients cannot afford this.”

Another cost-effectiveness analysis, which compared ibrutinib at its current price with chlorambucil, did not show that ibrutinib was cost-effective with any set of assumptions when given in the front-line setting.

Dr Brown maintains that young, fit patients with CLL and IGHV mutation should clearly receive the FCR regimen. “It’s 6 months of therapy for a possible cure,” she said. But young, fit patients with CLL without IGHV mutation, or older patients, can also receive chemoimmunotherapy (FCR or bendamustine plus rituximab).

“I agree with Bill that if patients are candidates for FCR, it’s clearly more effective and clearly has the potential for cure,” she noted. “But bendamustine plus rituximab can be effective in the older patients as well, and they can have prolonged remissions, even though you don’t see the same plateau.”

Discussing Dr Wierda’s argument that the crossover in these studies prevents us from seeing a clear overall survival benefit, she argued that novel agents work very well in the second line, but it is still unclear if chemoimmunotherapy will work after ibrutinib.

“So we may be losing a line of therapy if we don’t use it in appropriate patients early on as we manage the disease over their lifetime,” Dr Brown advised.

The treatment goal is time-limited novel combinations that reduce toxicity and maintain survival, according to Dr Brown. “Venetoclax plus obinutuzumab is definitely getting us closer than continuous BTK therapy in that it does result in undetectable MRD and high 2-year PFS, even after stopping therapy at 1 year,” she said.

But she added that “there are a number of limitations.” First, follow-up remains very short compared with the 10 years needed to rival the FCR cure for patients with CLL and IGHV mutation; the cost is still high; and the long-term complications of venetoclax are still unknown.

BTK inhibitors are now being combined with venetoclax, and although these are highly effective in inducing undetectable MRD, they are unlikely to be available to patients routinely in the near future, given their costs, she added.

“Chemoimmunotherapy is our only known potential cure—with FCR for the fit, mutated patients—and it can also result in prolonged treatment-free intervals for patients who are older,” said Dr Brown. “As we manage CLL as a chronic disease over a lifetime, we need to continue to have this in our armamentarium.”