

ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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Insights Into the Management of Older Patients With Multiple Myeloma



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H&O What is the age distribution among patients with multiple myeloma?

KA Studies have shown that the median age of patients with multiple myeloma is the mid to late 60s. Although there is a significant number of younger patients, multiple myeloma is considered a disease of the elderly. In multiple myeloma, we divide patients into those who are eligible for transplant or not. Transplant candidates have a physiologic age of 70 years or younger with adequate heart, lung, liver, and kidney function. In multiple myeloma, the term “older” often refers to patients who are not eligible for transplant.

The age distribution of patients has not changed. However, we are now diagnosing patients much earlier in the disease course. Many patients are diagnosed at the time of their annual physical based on results of abnormal blood tests, whereas in the past, patients were often diagnosed after they developed symptoms.

H&O Do treatment strategies differ for older vs younger patients with multiple myeloma?

KA Many novel treatments have been developed in the past 15 years; as a consequence, patients with multiple myeloma are now living approximately 3 to 4 times longer than in the past. However, most of the benefits of novel therapies have been seen in younger patients. The paradigm for the treatment of younger patients often consists of induction with a triplet regimen of novel therapies followed by high-dose melphalan and transplant, and then maintenance therapy with novel agents.

Older patients receive combinations of novel therapies and maintenance treatment, but they do not undergo transplant.

H&O What challenges are specific to the older population?

KA The main challenge is to ensure that older patients can receive the benefits of novel combination targeted treatments, given the morbidities that develop with age. Comorbidities such as diabetes, hypertension, and poor performance status must be considered. It is possible to adjust the dose and schedule of treatment for elderly patients depending on their comorbidities, in particular whether they are fit or frail. These objective scales evaluating the fitness of patients make it possible to adjust the treatments so that they are well tolerated even by frail patients.

H&O What types of dose adjustments or modified administration strategies are used?

KA In younger, newly diagnosed patients, we often use 3 drugs: the immunomodulatory drug lenalidomide (Revlimid, Celgene), the proteasome inhibitor bortezomib, and dexamethasone. In the elderly, we attenuate the dose and schedule so that this regimen is tolerated. In frail, elderly patients, we might choose to use 2 rather than 3 drugs, such as lenalidomide and dexamethasone. As noted above, there is increasing value placed upon evaluation of an elderly patient's physical status to determine whether he or she is fit or frail. The dose and/or

schedule of a particular regimen is then adjusted, so that each patient can appreciate the maximal benefit from novel therapies.

H&O Do adverse events differ in older vs younger patients?

KA The adverse events are of a similar type, but they can be more severe in older patients. For example, older patients tolerate dexamethasone poorly compared with younger patients. Dose reductions to avoid adverse events are probably more common with dexamethasone than any other drug in multiple myeloma. Another example is the proteasome inhibitor carfilzomib (Kyprolis, Amgen), which is very active in multiple myeloma. Carfilzomib is associated with a low incidence of cardiac toxicity, and this event rarely occurs in patients who are otherwise healthy. Among patients with underlying cardiac disease, which is more common in the elderly, this toxicity is more of a concern.

H&O Are there any supportive care measures for elderly patients?

KA There are supportive measures for all patients with multiple myeloma, to help manage complications of the disease and/or treatment. For example, the amino bisphosphonates, such as zoledronic acid (Zometa, Novartis), and drugs targeting the RANK ligand, such as denosumab (Xgeva, Amgen), can decrease bone complications. In addition, patients with multiple myeloma are susceptible to infection because of low immunoglobulin levels. Intravenous gamma globulin can be used in patients with low-normal immunoglobulin levels who have recurrent life-threatening infections. Prophylactic antibiotics can be useful (eg, acyclovir in patients receiving proteasome inhibitors), and hematopoietic growth factors can be used in patients with low blood counts, as in other cancers.

H&O Are there any treatments in development likely to benefit the older patient population?

KA There are many new drugs under development in multiple myeloma. These drugs will likely aid all patients, including those who are elderly. Promising immune agents include novel monoclonal antibodies, such as isatuximab. A novel immunotoxin therapy links the B-cell maturation antigen (BCMA) antibody to a toxin to deliver the toxin to tumor cells that are positive for BCMA. Perhaps the most exciting immunotherapy that might offer particular benefit to the elderly is a bispecific T-cell engager (BiTE). This off-the-shelf therapy binds to BCMA on the surface of

myeloma cells on the one hand, and binds to CD3-positive T cells on the other, thereby localizing the immune cells at the site of the myeloma. Responses have already been observed in early-phase clinical trials.

Chimeric antigen receptor (CAR) T cells are now demonstrating very promising results in early clinical trials, primarily in younger, more-fit patients. However, they may

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be useful in the elderly when efficacy, sustainability, and tolerability are improved.

H&O Are older patients adequately represented in clinical trials of treatment for multiple myeloma?

KA In clinical trials of multiple myeloma, as in other cancers, there is a need for better representation of all types of real-world patients. Multiple new drug registration trials have focused on elderly patients who are not eligible for transplant, but they often exclude patients with comorbidities. For example, clinical trials may exclude patients with renal compromise or other comorbidities. In particular, the elderly—who are more likely to have comorbidities—may be less accurately represented in registration trials than younger patients. It is important to realize that real-world outcomes are often inferior to those seen in clinical trials done for registration of novel agents. Fortunately, there are now trials comparing outcome in elderly patients who are fit vs frail, as well as an increased emphasis on tracking real-world outcome of novel therapies in the elderly.

H&O Do older patients express concerns about their disease that are different from those of younger patients?

KA Older patients often have different goals from younger patients. The older patients would like to have

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their disease controlled to the extent that they can live longer, while maintaining their quality of life. They are less concerned with achieving a complete response or minimal residual disease (MRD) negativity than are younger patients with multiple myeloma.

H&O Do you have any other suggestions for the management of older patients with multiple myeloma?

KA The main consideration is to realize that elderly patients can benefit from novel treatments, whether targeted agents or immunotherapies. Importantly, it is possible to attenuate the dose and/or schedule based upon the patient's status (frail vs fit), to individualize management. Elderly patients can then be treated with novel therapies and immunotherapies in the real-world setting, and they are likely to enjoy many years of benefit as a consequence. As exciting as the progress in multiple myeloma has been over the past 1 to 2 decades, the best is yet to come.

Disclosure

Dr Anderson is a consultant for Celgene, Millennium, Takeda, Bristol-Myers Squibb, Sanofi-Aventis, Gilead, Janssen, and Precision BioSciences. He is the Scientific Founder of OncoPep and CA Therapeutics.

Suggested Readings

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