Managing Myeloma

Planning Treatment Strategies for Older Adults with Myeloma: Considerations for Assessment of the Elderly/Frail Patient

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Learning Objectives:

- Describe the influence of patient age and the common comorbidities associated with the elderly/frail population when planning treatment regimens
- Employ current treatment guidelines and recommendations when devising therapeutic strategies for elderly/frail patients with myeloma
- Monitor and manage treatment-emergent toxicities with rapid and effective strategies to ensure optimal therapeutic outcomes and patient safety

Why is assessment of aging and fitness important when formulating management approaches for a patient with multiple myeloma?

The intensity of therapies used for treating multiple myeloma ranges from standard, low-dose chemotherapy, all the way to high-dose chemotherapy with autologous stem cell transplant (ASCT), which of course is one of the most aggressive interventions we employ in modern medicine. A more aggressive approach such as ASCT may do a better job of controlling myeloma and prolonging survival, but those more aggressive approaches also significantly increase the risk of toxicity.

The ability of patients to tolerate more aggressive therapy is largely driven by things like age, comorbidities, and their overall fitness. For example, young patients with a lot of reserve often do perfectly fine with more aggressive therapies compared to older patients who may have less reserve. Therefore, a major goal of individualizing therapy is to achieve a good balance between an approach that's aggressive enough to offer the highest likelihood of durably controlling a patient's myeloma, but that doesn't present the patient with an excessively high risk of severe toxicity, including even possibly death. Striking the right balance requires a richer assessment of a patient than just looking at their chronological age.

In what proportion of the multiple myeloma population are these issues of age and fitness a particular concern?

Myeloma is primarily a cancer of older adults, with an average age at diagnosis of about 70 years.[1] A good number of these patients are very old, even above 80 or 90, so themes that relate to geriatrics and the aging human are certainly relevant to this field. And as the general population grows older, the number of older people with myeloma is only likely to increase with time. We who work in myeloma full time are starting to wonder whether there will be enough myeloma physicians in the future to manage all of these patients that will have it!

What is currently the optimal method for assessing the impact of aging and fitness in older adults with multiple myeloma?

Until now the suboptimal standard has been the eyeball test. You walk into the room and look at the patient—maybe they roll into the clinic in a wheelchair, or maybe they walk in wearing running shoes because they just ran a 10K. We look at comorbidities that could limit their ability to receive therapy or tolerate toxicity. Age also plays a role, though hopefully all of us who treat any form of cancer, including myeloma, have moved away from making firm treatment decisions based on age alone.

In particular, stem cell transplant historically had fairly firm aged cut-offs—it used to be that no one over age 65 got a transplant. Then it was above age 70. Nowadays, especially here in the United States, there's much more a sense that age is just a number, as many older adults are perfectly fit and able to tolerate even maximally aggressive interventions such as transplant. We've published research on this saying that you can do transplants in older adults very safely and with similar effectiveness as compared to younger patients.[2] So there's an emerging consensus that we should look at age as one factor among many, and that we shouldn't exclude patients from even maximally aggressive therapies such as ASCT purely based on age.

But the optimal method for assessing the impact of aging is arguably geriatric assessment (GA), which we'll talk about later, but I'll briefly say that those assessments offer fairly comprehensive ways of evaluating the entire patient beyond just age, in ways that can likely help us to select the right level therapeutic intensity I mentioned earlier, for an individual.

How can older patients be evaluated more objectively?

The field is evolving toward the routine use of GAs. These are fairly practical questionnaires or other tests that can be done in the clinic to get a better sense not only of the patient's age and list of medical problems, but also how functionally impaired they are—can they walk? Bathe themselves? Go grocery shopping? Drive? Are they impaired by pain? Socially isolated? Do they have trouble seeing or hearing? How many medications are they on? A number of different factors go into the big picture of how robust an individual is, and in turn, how likely he or she is to tolerate specific therapeutic interventions.

At this point GAs have been shown to predict risk of toxicity and survival fairly well in multiple myeloma, and further studies are ongoing to determine whether GAs could even inform selection of therapy, including whether or not a patient should go on to ASCT, but we're not quite there yet.

Could you break down the findings to date on different geriatric assessments in multiple myeloma?

The largest study to date is a pooled analysis of 869 newly diagnosed elderly multiple myeloma patients by the International Myeloma Working Group (IMWG)[3] that was published in 2015 in *Blood*. Based on that analysis, the IMWG came up with a 5-point frailty score[4] based on age, comorbidities, and cognitive and physical conditions that predicted mortality and risk of toxicity. Fitness was broken down into three categories--frail, intermediate fit, and fit. There was a significant difference in 3-year overall survival, for example: 57% for frail, 76% for intermediate fitness, and 84% for fit. So this study provided proof of principle that GA predicts meaningful outcomes in myeloma.

One that we've worked with was developed by the Cancer and Aging Research Group (CARG) and was initially published in *Journal of Clinical Oncology* in 2011 by Arti Hurria and co-authors.[5] That's the seminal paper for geriatric assessment in cancer, primarily in solid tumors, though multiple groups have explored use of the CARG geriatric assessment in myeloma. We preliminarily tested the CARG in toxicity-vulnerable older adults who received a first-line regimen known as VCD-lite, a dose-attenuated bortezomib, cyclophosphamide and dexamethasone regimen.[6] A larger study led by my colleague Dr. Betsy O'Donnell at Dana Farber Cancer Institute that my center is collaborating on also incorporates CARG GA (NCT04009109) and will provide more data on this topic. There are a few others I can mention, including the Carolina Frailty Index (CFI), which is a 32-item index developed using cancer-specific GA data that was found to be predictive of all-cause mortality in older adults with cancer.[7] Another is the Revised Myeloma Comorbidity Index (R-MCI),[8] which may have some advantages over commonly used comorbidity indices in terms of the accuracy of assessment, but it's fairly complex.

Which of these instruments is best suited to the assessment of an elderly patient with multiple myeloma?

Based on available data, it's not really clear currently which of these instruments is the best. Ideally, you would simply pick any one system, and it would identify patients as fit versus frail just like the other instruments. The problem is that when these are looked at comparatively, they don't necessarily overlap, meaning for example that patients who are characterized as frail by the CFI are not necessarily characterized as frail by the CARG. We recently published a comparison of the IMWG, R-MCI, and CFI and found that out of 28 myeloma patients classified as frail by at least one of these models, only three were categorized by frail by all three of the models.[9] So you're looking at identifying different groups of frail patients—which is still relevant but makes incorporating this into routine clinical care trickier.

Based on evidence to date, is there any value in routinely incorporating geriatric assessment into in clinical decision making? What are the benefits?

Geriatric assessment can definitely be used today in clinical decision making. The American Society of Clinical Oncology (ASCO)[10] and the International Society of Geriatric Oncology (SIOG) both have published documents that affirm the value of GA and encourage clinicians to employ them routinely, not just as part of research studies.[11]

The value of GA is to give the treating clinician a sense of the likelihood of severe toxicity and whether the patient is likely to tolerate therapy. GA also can identify relevant deficits that we might have missed otherwise, such as malnutrition, falls risk, or social isolation. Identifying those problems could prompt helpful referrals to the nutritionist or physical therapist. More directly as it impacts therapy, someday we'll be able to use GA more objectively to help us predict therapeutic toxicity and in turn make decisions about how aggressively to treat individuals with myeloma, but we're not quite there yet. That said, GA is fairly well proven now to do a better job of risk-stratifying patients than we do as clinicians without the use of such instruments—basically, the eyeball test is not as good as GA.

What goes into your thought process today when you are considering specific treatments for older patients with newly diagnosed multiple myeloma, both in terms of the efficacy you are hoping to see and the toxicities that you are trying to avoid?

It really comes down to data we get from age, comorbidities, and GA. We consider all those factors to get a sense of how well we think a patient will tolerate toxicity in general. We then look at the unique toxicity profile for specific therapies as we choose a specific treatment regimen. Ideally, we choose a treatment regimen that doesn't overly stress a patient's existing problems. For example, diarrhea is one of the primary side effects of bortezomib.[12] Moderate diarrhea may not be a big deal to young, healthy myeloma patients, but for older patients who are more sensitive to volume losses and can't tolerate dehydration, the diarrhea may pose a real danger. And on top of that, if they have osteoarthritis or otherwise have limited mobility, that then may turn frequent, quick trips to the restroom into a falls risk. That same diarrhea that was no big deal for the younger adult may become life-threatening for an older, frail one, resulting in hospitalization or at least severely impaired quality of life.

Another good example is carfilzomib, which causes hypertension and heart failure in a small number of individuals.[13] For older patients who may have coronary artery disease or even congestive heart failure to begin with, it may not take as much of that drug to induce decompensation of that heart failure, which again can prompt hospitalizations.

Then another side effect that we think about commonly is peripheral neuropathy, which is associated with certain agents that we use to treat myeloma. We've figured out ways to minimize peripheral neuropathy, but it's still an issue. For older adults already at risk for falls due to issues I mentioned earlier, when you add numb feet to the mix, that can really increase the fall risk. Of course, a fall and a hip fracture or an intracranial bleed could be life-threatening.

These issues are generally much easier to prevent or manage while they're mild, but once they progress, they can be debilitating or even fatal. I often tell fellows that when it comes to chemotherapy regimens, picking the recipe out of the cookbook is easy—it's baking the cake that is the hard part. Picking a treatment regimen is easy. It's getting the patient through that treatment that's the hard part. We are sometimes walking a fine line, especially in older patients, to manage toxicities and keep them on the treatment so that their disease is well controlled. So it helps to have a good awareness of the toxicities with these drugs and how to manage them if they come up. I also can't stress enough how important it is to optimize supportive care through prevention of side effects when possible, and intervening early when problems come up, before things really fall apart.

Can using the "lite" treatment regimens for multiple myeloma help optimize the balance between efficacy and safety for older, frail patients?

We've known for a long time that many patients, especially older adults, often can't tolerate full doses of agents used in the treatment of myeloma in clinical trials. For example, some elderly patients will require reduced doses of lenalidomide because full dose as published in the literature may cause them excessively low blood counts, fatigue or diarrhea. That just highlights the fact that published studies are frequently not entirely relevant to very old, frail patients with myeloma being treated in the real world. Many patients we see in clinic are not pristine clinical trial candidates, rather, they come with comorbidities. They would often not be included on the trials that are published and get treatment regimens approved.

With that in mind, the idea behind the “lite” regimens like RVD-lite, VCD-lite, and others, is that we modify the standard-of-care regimens in ways that, hopefully, preserve efficacy but reduce toxicity, especially in older, frail patients.

Some of the modifications are built upon studies demonstrating that giving bortezomib once instead of twice a week, and then similarly, giving it subcutaneously instead of intravenously, result in about a 30% reduction in gastrointestinal toxicity and peripheral neuropathy.[14,15] So both RVD-lite and VCD-lite exploit that by giving bortezomib subcutaneously and once a week, instead of, again, the historical standard of twice a week intravenously.[6,16]

Often these regimens involve reduced doses of lenalidomide, reduced doses of dexamethasone, or longer breaks between treatment periods, again, with the overall goal of making those regimens more tolerable for older, frail adults while hopefully preserving the efficacy.

What we do not have are large-scale studies to evaluate these regimens. Ideally we’d have randomized studies that would, for example, compare full-dose RVD to RVD-lite to see if the lite regimen really reduces toxicity while maintaining efficacy as measured by, say, progression-free survival. Those studies have not been done and they’d be challenging to complete. Nonetheless, the “lite” and other relevant regimens as published are very promising and we routinely do use them in older frail adults. From my own practice I can say that they often work well and are well tolerated, even in patients with limited ability to tolerate toxicity.

In closing, what is the most important advice you would give to a community physician who is concerned about walking that fine line between treatment efficacy and toxicity in their older, frail patients with multiple myeloma?

Be aggressive about preventing and then managing toxicity when it starts. Younger, healthy patients have more reserve, and so they can often better tolerate side effects, but older adults may really have trouble tolerating the homeostatic upset that comes with chemotherapy toxicity. Early intervention is critical. In our practice, when we start a patient on a new treatment regimen, we’ll see them on cycle 1, day 1, and then again on day 8 or day 15—very early, and ask them how it’s going after the first few doses—how are their bowels, their energy levels, are they noticing any side effects? Are they eating OK? Thinking clearly? If problems are starting, we can intervene very early and hopefully before toxicity becomes severe.

Prevention is also really key. A great example is the use of daily valacyclovir, which is very effective and therefore standard of care in preventing herpes zoster in myeloma patients receiving proteasome inhibitor- or monoclonal antibody-containing regimens.[17] It’s an easy thing to do and incredibly important, because anybody who's seen it knows that bad shingles can be really terrible and permanently disabling. Similarly, blood clots are very common, and so thinking about thromboprophylaxis is critical. Just be vigilant about toxicity and remember that supportive care is as important as choosing treatment regimens when we consider our role in getting patients through these regimens in ways that, hopefully, maximize longevity and quality of life by both controlling myeloma and minimizing side effects.

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