Managing Myeloma

MRD and Risk-Adapted Treatment in Multiple Myeloma

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Overview

Welcome to this issue on minimal residual disease (MRD) and risk-adapted treatment of multiple myeloma. The main topics of this issue will be the clinical implications of MRD and its use in guiding treatment decisions. How risk-adapted treatment benefits patients and the work that still needs to be done in the multiple myeloma arena will also be discussed.

How is MRD-negative status measured or defined, and what level of MRD is considered MRD-negative?

Myeloma is a very complex disease. It is a blend of a liquid tumor and a solid tumor. We have a lot of other diseases that are leukemias where there's good precedent for MRD testing, often in the blood or the marrow, but those diseases lack osseous, or solid tumor components. Myeloma can quite often have osseous components or extramedullary components. Therefore, we should be thinking of MRD as a tool in our arsenal to measure response.

Historically, we've gone from serum protein electrophoresis (SPEP) to urine protein electrophoresis (UPEP), to urine immunofixation, to light chains, and radiologic imaging. When you've done all of that, that's where MRD has value. When the therapies keep increasing, your diagnostic tools must keep up. We have some newer technologies, but historically, MRD was being done from a bone marrow aspirate, either by next-generation flow or next-generation sequencing. Deeper is better, so 10^{-4} is not as good as 10^{-5}, which is not as good as 10^{-6}. The goal would be as deep as you can get. There are some emerging technologies that are even claiming 10^{-7}, so either 1 in a million or 1 in 10 million cells of myeloma. The other important part is to sustain the MRD negativity.

What are the clinical implications of losing MRD-negative status?

We must keep in mind that MRD is a surrogate endpoint. Overall survival (OS) is number one, progression-free survival (PFS) is number two. Then we have these other surrogate endpoints, which are response-based tests. Whether it is serum assays, urine assays, light chain, or MRD. What we must recognize is that we do a lot of risk stratification of patients at baseline before they're treated.

Regardless of whether a patient is high-risk or low-risk; if they are MRD-negative, that clearly has prognostic value. They are going to do better if they’re MRD-negative, but they must sustain that. The sample could be negative the first time due to a poor sample and then positive at the second test. This possibility must be borne in mind. The second scenario is if the patient truly is MRD-negative. If it was a good-quality test and they’ve lost MRD-negativity, that suggests that there is biology that makes this disease more aggressive. We're recognizing that in myeloma, this so-called

functional high-risk myeloma is not well appreciated. We know, for example, in prospective clinical trials, that when people enter with symptoms, they're going to have a worse prognosis than those who are entering with asymptomatic disease. CRAB symptoms, calcium, renal, anemia, bone; people who have those as opposed to somebody who has just purely biochemical progression is going to have a different outcome on the study.

In the SWOG study, patients received any induction therapies prior to getting a transplant, then were randomized post-transplant to lenalidomide plus daratumumab or lenalidomide alone. MRD was then assessed at two years, and MRD-negative patients were randomized to either continue or cease therapy; helping us to see if patients can cease therapy if they get to a deep response. Please could you comment on MRD as a measure of deep response in multiple myeloma?

This SWOG study is about moving from a prognostic test to a predictive test, and I think that's an important topic. If a patient is told their prognosis and they have high-risk disease, that's disheartening. What's more important is what are we going to do with that?

A good example of moving from a prognostic to predictive test in myeloma is translocation t(11:14). We now know that if you have that translocation, there's a particular drug, venetoclax, that's exquisitely sensitive for these patients with myeloma with that t(11:14). Then we're going to incorporate that drug into the treatment. Conversely, with just MRD, it's hard to know what to do with that because most of the studies to date have been prognostic, not predictive.

What that means is patients who do better, do better. If you're MRD-negative, you're going to do better than if you're MRD-positive. The question is, can you convert people from one to the other category using therapies? That's what this SWOG study is trying to determine; if there's MRD-negativity, is it appropriate to discontinue therapy?

What is the use of MRD in guiding treatment?

If patients are living longer, we need to start asking the question whether everybody needs to be treated forever. Historically, when you have an incurable condition, and the data was always treatment to progression, we never discontinued therapy on anybody. Now at our site, for example, some patients have been off therapy over 5 years without relapse. I think we are curing about 10% of patients.

Until we have prospective, risk-adapted randomized studies like the SWOG study, this is how some clinicians currently use MRD in the real world. It's these extremes of patients where if I have a high-risk patient, I want to make sure they're MRD-negative and staying there. If it's a low-risk patient, especially if they're having side effects; we must recognize that the danger of discontinuing therapies in low-risk patients is that these might be the patients who benefit from therapies. Part of what makes them low risk is their sensitivity to therapy.

Before we discontinue therapy on patients, we need the prospective data. Certainly, if somebody has standard-risk myeloma, and is having side effects from treatment, which can also include financial toxicity, discontinuing therapy should be considered. We should be using MRD to guide treatment. We need prospective risk-adapted randomized studies to take this test from a prognostic test to a predictive test.

What are your views on the use of MRD-negativity being used as a primary efficacy endpoint in clinical trials to establish efficacy?

There was an important meeting this year from the FDA and International Myeloma Society to talk about drug development endpoints. Regulatory agencies are open to the discussion of MRD as an endpoint, but they want more data. I think I support that. We in academia have not done a good job with presenting the data.

I think we need to have that balanced approach about the urgent need for this test to get approved as a regulatory endpoint, but we're far from doing all the work that's needed to satisfy statisticians and regulatory authorities that this ***is*** a meaningful endpoint.

Please outline the use of MRD-negativity as a guide to cease maintenance therapy? How long before we can cease maintenance once MRD-negativity is achieved?

In the MASTER study, the aim was to determine whether we can start discontinuing therapies. Quadruplet therapy was used; D-KRd (daratumumab, carfilzomib, lenalidomide, and dexamethasone), a quadruplet induction of the most potent agents in each class for newly diagnosed transplant-eligible myeloma.

Appropriately, they did not make any decisions on one MRD time point. They waited for two MRD time points. At various points along the continuum of treatment, whether it's after transplant, consolidation, or maintenance, patients could discontinue all therapy if they had attained two MRD negativities consecutively. In that study, what we found was that the high-risk patients at current follow-up, especially those who had two or more cytogenetic abnormalities, relapsed very early. We're not seeing that with standard-risk.

For community doctors who are treating a lot of different cancers, it can be difficult to keep up with all this data. Hopefully, we can shed some light on why MRD is lagging in myeloma, perhaps compared to some other malignancies. It's because of all these complexities, and we have other serologic techniques for following the disease.

Early relapse is linked to reduced survival, even after an intensive first line of treatment. The first line of treatment in multiple myeloma is considered crucial to prolong the duration of response and survival. Similarly, patients who do not achieve long-lasting MRD negativity are also considered high-risk. Has MRD negativity become the new benchmark in the treatment of multiple myeloma?[1]

If we think about not just baseline risk stratification, but a more response-adapted risk stratification, the worst is primary refractory, where patients don't respond to initial therapy. Next comes early relapse when a patient responds, but then relapses. Then the third is the lack of MRD negativity. It's not as bad as the first two categories because MRD is not meaningful if a patient has not responded to treatment or is experiencing a resurgence of the disease.

One of the dangers of using MRD is that of interpretation. In places where fluorescence in situ hybridization (FISH) is not available, a patient may be at high-risk, and the clinician may not know that. Just because there is a new test doesn't mean it should always be used for treatment decisions, because there is a data gap. Clinical trial versus real world is an important distinction.

Transplant-eligible versus ineligible is also important. If you have a frail, elderly patient, you want to get the MRD negativity, but not at the expense of toxicity of the treatment. The patient must be tolerating the drugs. We wouldn't be using a 5-drug regimen in a frail, elderly patient. Clinical trial vs real-world, the frailty of the patient, the patient's clinical features, and the risk status of the patient, are all important factors in whether it is a benchmark or not. Hopefully, it will become a benchmark in standard of care in the future, but right now I think we have more work to do.

Should we adjust medication to achieve MRD-negativity, even if the patient is in a complete response (CR)?[2]

Prognostically, many studies have shown that a CR without MRD negativity is not as good, and patients without MRD negativity will not have as long a remission. It's clear across multiple datasets that MRD negativity has prognostic value, but then whether treatment should be changed is a predictive question. We need the prospective randomized studies to answer that, which we don't yet have.

In a high-risk patient who is not attaining MRD negativity, I do sometimes try to do more for that patient, whether it's more consolidation, more maintenance, or extending the duration of therapy. Because although we don't have prospective data, this is a high-risk patient who has not attained MRD negativity, which has negative prognostic value for the patient. If there's something that I can do that isn't going to be toxic, then I'll certainly try to do that.

Briefly discuss the concept of risk-adapted treatment with regards to multiple myeloma?

In comparison to lymphoma, where there are different histologic subtypes which are treated differently, myeloma is not sub-categorized. We call myeloma a single disease. We know that there are frail patients, elderly patients, and patients with persistent renal failure. There are no high-risk features, one high-risk feature, or multiple high-risk features. Yet, all these patients are being treated the same.

For me, risk-adapted treatment means personalized therapy. You stop treating myeloma patients all the same, and each person is getting individualized therapy, both based on their initial profile, but also how they respond to therapy in more of a functional and dynamic fashion.

One of the controversies that limit risk-adapted treatments in multiple myeloma is the challenge of defining the high-risk patient. Stratifying patients into different risk groups depends on several aspects. Molecular abnormalities are one way to determine high risk, but the clinical behavior of the patient is another one. In your opinion, what is the most important factor in patient risk stratification?[1]

If we think about survival curves, which is ultimately what this is all about; in myeloma, we have not yet gotten to a flat survival curve. Some people say that the definition of cure in a disease is that the OS curve for a patient should track with their age-match counterparts. I don't think we've gotten there for all myeloma patients. We have gotten there for a subset of patients, and the way we've been doing that is by the iterative improvement of risk stratification.

We know if a patient is frail, elderly, or has renal failure. Whether it's reversible, is unknown at baseline. We treat the patient and see if their kidney function improves. If they have extramedullary disease, that can be something we know at baseline, but sometimes that evolves and emerges with treatment. Molecular abnormalities are known at baseline, but they also change. More high-risk

features can present as you treat patients over time. Whether they are multidrug refractory is something we don't know at baseline. Before you've treated somebody, you don't know if they're going to have primary refractory myeloma, but if after a few cycles of therapy, they are refractory, that's ominous.

We have baseline risk stratification, and there's also functional or dynamic risk stratification for which you need to see what happens after you start treatment, hopefully the best treatment you can offer your patient. Then based on that, therapy can be changed in the future. One of the limitations, however, is that this so-called functional and dynamic risk stratification is not rigorously being done. In this dataset, probably 20% to 30% of relapse myeloma patients are functionally high-risk in some capacity. Either they're primary refractory or relapse, loss of MRD negativity, or they have another risk functional feature, and yet we are not stratifying by that.

Closing thoughts

We're curing ever-increasing numbers of patients with myeloma. If we don't get better diagnostic technology, we are not going to be able to continue therapies on those cured patients. Conversely, we're not going to be able to improve as quickly for the high-risk patients. It's an important area to be focusing on. Myeloma has made tremendous progress. The reason for this progress is because of collaboration. I think collaboration will help to move us forward. The key stakeholders are, first and foremost, the patients and their caregivers that are at the center of this, but with that are academia, the health regulatory agencies such as the FDA and EMA, industry partners, nonprofit agencies, and educational companies.

We need to work collectively to advance the field. There has been a lot of progress in a short time, and advancement won't come with just one stakeholder. It's going to take these iterative meetings and collaborative efforts to really make an impact.

References:

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