Managing Myeloma

Defining Smoldering Myeloma: Controversies and Impact on Treatment Selection

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Dr. Chari: We have all of these new treatments and we're able to diagnose patients early and the treatments are getting very effective with very limited toxicity and so the question is, do we need to wait for the CRAB symptoms? There's always this evolving group of people in the IMW that seems to want to keep chopping up things into more and more smaller subgroups. One of the latest efforts to risk-stratify smoldering is called the 2/20/20 system, which is basically looking at the M-spike greater than 2, bone marrow more than 20%, and the free light chain greater than 20. The question being asked here was that, based on the SLiM CRAB criteria, which is again, going back to that free light chain greater than 100, marrow greater than 60%, and MRI greater than one lesion, the idea of the SLiM CRAB was that if patients have an 80% or higher likelihood of progression at two years, why are we waiting for CRAB symptoms? We should treat, and so that seems like an easy no-brainer, although that's still fraught with issues. But that was the initial intent that we don't need to wait for CRABs and since we can identify potentially a group of high-risk patients, let's just start treating those and that became SLiM CRAB and everybody who drinks the Kool-Aid started treating that.

Now, the same group of people who like to chop up smoldering, want to chop up the remaining non SLiM CRAB into further identifying who's high risk, and this was that effort and appropriately showed that as you might expect, higher M-spike, higher marrow greater than 20%, and light chain more than 20; light chain ratio, and that's involved over uninvolved. This came up with a progression at two years of about 50%, so that was the new smoldering. I'm curious to hear your take on it, but my whole take on the smoldering categories is I feel like movies are more interesting than photographs. And I don't see the need for everybody to just take that photograph at baseline and suddenly make lifelong treatment decisions on the basis of one single timepoint, and this is not a patient population that is actively symptomatic. We are not yet curing these patients. All drugs have side effects, including cost as well as medical side effects and psychological side effects. But to me, the question is really, I think we agree that if there's truly a high-risk patient population that we can reliably and reproducibly predict across the world with the same system, then it makes sense, but I think for me, if you can't even reliably agree on who is truly high risk, we shouldn't be treating on the basis of a photograph. And I'll speak more to the movie part of it because we've done some work on that. But do you do movie or photograph?

Dr. Richter: I couldn't agree more that photographs is the incorrect way to go, that movie is the reality. In 2014, we had to change the SLiM CRAB criteria, now we have this. And there were patients that I've been following for years prior to that, that would have been reclassified as

having active disease, and the conversation I had with them was the criteria changed, the biology of your disease did not. So, people who fit these criteria don't necessarily need to be treated. The advantage of the SLiM CRAB is for people on the precipice that we know need to be treated, it now allows us to treat them, but I completely agree on a one-time snapshot if they meet those criteria, I most commonly do not treat them at all.

Dr. Chari: I think that's the real complexity, particularly for a community doctor who may not be seeing a lot of myeloma patients, feeling this need to immediately treat based on a free light chain greater than 100. We did a study that's been published in *Blood Advances*; we took about 275 consecutive smoldering myeloma patients and followed them over time, and we looked at the SLiM CRAB and in our hands, the risk of progression of all of those was not 80% at two years. In our hands the free light chain greater than 100 was only about 40% predictive at two years, and even marrow greater than 60%, which sounds very scary, but remember that these are people who have normal hemoglobins. We have to remember that myeloma can have patchy involvement of the marrow. So if you have a spot of marrow that you hit, and it's very rich with plasma cells and it is 60%, but the hemoglobin is 14, month after month after month, year after year, could it be that you hit a high patch of disease? And so I think we always teach medical students, don't treat the number, treat the patient. And I feel like we're going into this treating the number thing and treating these photographs without reading and I think the other important point is that a lot of these studies are done retrospectively and there is tremendous value in doing prospective studies, and a good example, the only prospective study looking at free light chain ratio, which is from the Danish group, showed that the risk of progression in a prospective study of FLC greater than 100 was only 30% at two years. I think we can all agree 80% prediction at two years is scary and we should be treating, but if you can even consistently show that any of the SLiM CRAB criteria are 80%, then this to me, 2/20/20, is even more concerning for potentially people starting therapy. And the other big danger of the SLiM CRAB, we should mention, we talked about free light chain, so in our hands, not only did free light chain and marrow greater than 60% not show up in multivariate analysis, what did show up we're evolving things and that goes back to the movie. So patients whose M-spike are rapidly increasing, the hemoglobins are dropping, the light chains were increasing. It's the kinetics of the disease, the concerning movie, that's more important than what you started off with, and so I think my concern about a lot of these risk stratification criteria, people may start treating these patients and then we're excluding the very people that we probably should be putting in smoldering studies. Because we can't reliably predict who's getting myeloma. and then the other thing that people don't talk about enough is, what is the impact of the health care system? If you're going to start treating patients early, especially with an IMiD-based regimen, now you have to mandate collection of patients that didn't even need treatment, and then do you have to do the transplant? And so I think we'll talk about it in some studies. But I think these are some of the questions we have to wrestle with. It's not just can we use the drugs, but are we going to help patients with progression-free survival, but more importantly, overall survival? Because if we're seeing secondary cancers, cardiac issues, how is this going to impact these healthy patients?

Dr. Richter: I couldn't agree more. I think the 2/20/20 rule is a nice bedside tool for many of our colleagues who don't see as much myeloma on a day-to-day basis to get a gestalt of is this patient going to be extremely high risk of progressing or not? But I share all of your sentiments. To me, even the term smoldering myeloma is still kind of an arcane term. To me, there's a line in the sand. There's people who clearly need treatment now and people who do not and until we

have either evidence of how we can go about curing these patients or obvious ways to deepen durable remissions by minimizing all the toxicities, we have to be very careful about treating patients based on this alone.

Dr. Chari: I think in the future, we may actually eliminate smoldering, it may just be MGUS and myeloma, and we will know who better. I think the two other points to make is that (1) we've seen some studies that patients who have smoldering background actually have a better overall survival compared to patients who do not have a smoldering prodrome. If we go chasing patients to MRD negativity for that MGUS clone that is irrelevant, that's concerning, (2) and then the other point, I think, especially for a community person who may not see a lot of patients, is it's not just myeloma and MGUS, we have to remember to rule out other plasma cell disorders that can be mislabeled as MGUS and smoldering, including amyloid, POEMS syndrome. So anybody with neuropathy, renal dysfunction really needs due diligence to make sure we're not missing something that should be treated.

Dr. Richter: Absolutely. One of the interesting trials I'm really interested to hear your thoughts on is the CAESAR trial. This whole notion that we've had many trials that have been presented including the ECOG study about treating some of these patients with either lenalidomide or lenalidomide and dexamethasone alone, kind of the low levels of treatment; however, I think it was a very interesting trial saying, if the way we treat symptomatic disease is multi-agent chemotherapy with and without transplant, what is the role of that type of approach in smoldering? And I'm really interested to hear your thoughts.

Dr. Chari: We spent a little bit of time talking about who is the patient population to treat for smoldering and then the second part is what should you treat with. You alluded to one approach was the len-single agent per the ECOG study. This is the other extreme, this is called the CAESAR study from the Spanish group and this used KRd induction for six cycles with transplant consolidation and lenalidomide maintenance. This was for high-risk smoldering myeloma patients. Of course, the results are very impressive, response rate overall was 98% alive at 30 months, 93% of these patients were in remission, and over half were MRD negative, at 10^{-6}. I think that's really exciting and it brings up the question of can we cure? And certainly this is a very powerful regimen, but I think the question is we have to think about risk/benefit, cost again, and so there were some adverse events including infections, cardiac issues and then of course, it goes back to, this is a single arm study, and the question would be, what would be the control arm and how would that look? Because some of these patients were not even consistently high risk. Because we all agree the primary endpoint of every study should be overall survival, recognizing that it's a challenging endpoint, PFS would be a surrogate followed by MRD negativity as an earlier surrogate; but I think the real question would be, if we subjected a lot of these promising single arm studies to randomized studies in the smoldering setting, how would they do? And it goes back to if you don't pick the right patients, what if the control arm does really well? You may be grossly under power to show a difference, but I'm curious, would you, are you implementing CAESAR in your clinic?

Dr. Richter: Not quite yet. I think that if we are able to get sophisticated enough in the next period of time to really have, from a genomic and immunologic standpoint, to know who is really at that ultra-high-risk of progression and not simply based off of a bone marrow showing a certain amount of plasma cells or free light chain. But as we begin to understand more the

biology of these ultra-high-risk patients, I believe, yes, we should take a multi-agent approach because in my mind, the single agent approach, if you think about people either as active plasma cell dyscrasias or not, if they have a more benign course you're giving chemotherapy to people who otherwise don't need chemotherapy. And if you're saying these people should be treated as if they have active disease, when the standard of care is to give three or four drugs, then you're undertreating them with only one or two drugs. I do feel that at some point, this may be ready for primetime for certain patients but I don't think we're quite there just yet. And one of the points you brought up earlier, which I think is a really important point, is this concept of treating everyone to MRD negativity. MRD negativity is a really nice endpoint for trials as a surrogate for progression-free survival, as a surrogate for overall survival in attempts to get drugs approved by the FDA sooner. But that doesn't mean that we necessarily need to treat everyone to MRD negativity. There's some really fascinating data coming out of Bruno Paiva's lab about converting people to an MGUS-like phenotype. So ultimately, you don't necessarily have to treat everyone into no measurable disease, but we may have the genomic analysis in the future to say the disease that remains is fine, just leave it alone.

Dr. Chari: I really like what you're saying about the genomics biology because all these numbers and risk classifications are so binary. What makes 2.5 mg of an M-spike different than 1.9? And if you're 1.99, what does that make you? I mean, these are very silly to me. There's not science behind it and genomics, we've studied a lot. We know that the genomic changes that are occurring in myeloma are seen throughout the continuum, even in MGUS and smoldering, so it is neither necessary nor sufficient to have certain genomic alterations. And as you alluded to, also, the immunology is very important. It is not just we look at the tumor cells, but what about the bone marrow microenvironment? I think to really get that first part of the question right is, who needs to be treated? We need to understand the biology and then that will guide these treatments and absolutely this is a great option. If we can truly be confident that the people that we are treating, we're definitely going to progress and now we've achieved such great depth and duration of response, that's really exciting. But we don't how these people would have done with no trial therapy.

Dr. Richter: That's fascinating stuff. One of the interesting partners of this study looked at using a very fascinating technology using quantitative mass spectrometry to evaluate the clones along the way, and I'm really interested to hear your thoughts on is this something that we're going to start using on a regular basis to manage our patients or what do you think the future is?

Dr. Chari: I'm really excited about this technique because it kind of feels like the days where if you had an M-spike and you think an M-spike of zero is enough, and then you found out the IFE was positive, and then when that was negative, you find out the light chain ratios were abnormal. And so as we keep deepening our therapeutic responses, we need the diagnostic technology to keep up and one of my pet peeves about all the MRD studies is they never sample everyone. They only sample suspected CRs and going back to our sampling issues in myeloma, so what if your marrow is negative, if you still have positive M-spike or light chains or PET scans, especially the radiology techniques, and it's very important when doctors are looking at these MRD studies that you look at, these are clinical trials where there's rigorous testing of all the serologies, there's rigorous imaging requirements, and then you go to the marrow. It's very bad to go straight to the marrow when you still have osseous disease. And I think what's good about this mass spec is that now this is kind of like the cool CSI TV shows,

why are we using these old technologies, if CSI can use mass spec to pick up toxicology results, I think we should be doing more for our patients. And these tests are showing in a blood-based assay that you can detect paraproteins at a very small level, some studies are saying $1:10^{-6}$ or 10^{-7}. I think we need more data, but I think the key benefit of this is that this is saving our patients from an invasive procedure, which has a lot of limitations of the sampling and the quality of the aspirate and how quickly you get it to the marrow. I think what we learned from this study is that first, the mass spec would have avoided a lot of marrows and so if you're mass spec positive why are we subjecting them to the marrow? At least wait for that to be negative. The more complicated question is what if your mass spec is positive and your MRD marrow is negative? And there I think we need a little bit more follow up. But my prediction would be that probably the mass spec would win because of the sampling issues of the marrow. But I think going forward, once we have better validation, and this test is still under investigation, but once it's FDA approved or CLIA certified, then I think the workflow would be standard blood and urine testing followed by mass spec and then if that's negative, then it's appropriate to do the marrow. I think that will be great for patients, what do you think?

Dr. Richter: I couldn't agree more. This is really, really exciting. I think one of the things you brought up is the most important thing is patient quality of life. The ability to avoid a bone marrow. Patients are begging for this. They can't wait until everything to be done in the blood.

Dr. Chari: No patient has asked for a bone marrow.

Dr. Richter: The other advantage of this is as monoclonal antibodies like daratumumab and elotuzumab and future antibodies come on the market, we always have the concern for interference with our immunologic tests like the immunofixation. The benefit of the mass spec, as you and I talked about previously, is that you can pinpoint what is the drug and what is their disease, so it allows a way to get around some of that confusion.

Dr. Chari: Yes, very exciting.