

## What are emerging perspectives and strategies in the early intervention of smoldering myeloma?

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We have made a lot of advances in the treatment of multiple myeloma, and the landscape of treatment for myeloma continues to increase. The obvious question here then is, “Can we cure multiple myeloma?” When you start thinking about curing myeloma, you want to start early, because that would be the time when you can actually cure a substantial patient population. The good news in myeloma is we do have a precursor disease state, and that is called smoldering multiple myeloma. Now, smoldering multiple myeloma essentially meets all the criteria for multiple myeloma, but patients are not symptomatic and do not actually require therapy. What is happening today is that we are using that space to study a lot of different approaches. We are doing minimalistic approaches, and we are going to the absolute extreme and seeing which of these strategies will help get rid of progression to multiple myeloma. What we are using in the context of clinical trials essentially is patients who are at a higher risk of progressing to multiple myeloma and that can be dictated by the amount of plasmacytosis, the amount of monoclonal protein, the amount of serum-free light chains, and so on and so forth. We have built those criteria in to clinical trials. What we are doing at my institution is using a vaccination strategy, so that is more of a minimalistic approach. We are giving patients six doses of this vaccination strategy, followed by a booster at a couple of time points. The idea behind doing this vaccination strategy is almost like the analogy would be a flu shot. You give a patient a flu shot, you immunize them against the flu so that they do not get the flu. What we are doing here is we are giving them this vaccine called Pvx-410. It recognizes myeloma cells (XBP1, CD138, and SLAM-F7 – all known targets for multiple myeloma) the idea being, by doing so, that we are priming the T-cells, we are activating the T-cells. We have studied this in a subset of patients, about 22 patients already, and we were really reassured to see that when we first used the vaccine alone it is very safe; and when we use it in combination with lenalidomide, we were able to augment the responses of lenalidomide, of the vaccination, and we were able to see memory T-cells. Memory T-cells are those T-cells who have recognized the tumor as foreign and remember that it is foreign and work against that tumor. Having memory T-cells is actually a good thing and our hope is that those memory T-cells will keep the myeloma in check from progressing. We are just about starting to do the next phase of the trial wherein we are doing not just the lenalidomide but we are using other immunomodulatory strategies. In this case, we are using HDAC6 inhibition to see whether we can further augment this immune approach. This is at one end of the spectrum. At the other end of the spectrum, you have an approach like what was presented at last year's ASH; the GEM-CESAR study presented by Dr. Mateos. What they are doing there is, again, the same patient population, high-risk smoldering myeloma, but treating them as if they have multiple myeloma. They are using carfilzomib, lenalidomide, dexamethasone (a triplet-combination), getting them into remission, transplanting them; so using all drugs to get rid of disease completely to see whether or not we can change the natural history of the disease.

Along this spectrum, there is a whole bunch of other clinical trials which are out there, and if you go on to *Clinicaltrials.gov* you are going to see a whole host of these trials and the different permutations and combinations of these various trials. I think you are going to see responses in pretty much every trial that you see. I think the biggest issue is: are we going to be able to prevent that progression to multiple myeloma? We just do not have data to speak to that, but this is a very interesting field. It is a field where we are doing a lot of research with the intent of getting rid of multiple myeloma completely. Until these trials are all read out, the standard of care for patients with smoldering multiple myeloma – even today – should be no treatment and watchful waiting, the way we have been doing it routinely.