Myeloma News From ASH 2018: Encouraging Clinical Trial Updates From Dr. Ajai Chari

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Andrew Schorr:
Andrew Schorr on location at the ASH meeting, American Society of Hematology. We're here in San Diego. We're talking about myeloma, but myeloma certainly for people more advanced. Maybe they've had many treatments before, and there's new research coming out. What could be options for them?

With me is Dr. Ajai Chari from Mount Sinai Medical Center in New York. So you presented some data here. Help us understand what it means for families and patients who maybe have been through so much with myeloma.

Dr. Chari:
Sure. The scope of the problem is really quite important. So currently we have five major drugs, if you will, bortezomib (Velcade), carfilzomib (Kyprolis), lenalidomide (Revlimid), pomalidomide (Pomalyst) and daratumumab (Darzalex), and when patients become refractory to these agents there's really no approved therapy. And when each of these drugs were approved and particularly the most recent second-generation compounds of carfilzomib, pom and dara, they each had a response rate of around 25 percent progression-free survival of three-and-a-half months, which, while important and encouraging, that's not great.

And so these drugs are often combined and put together, but eventually patients still relapse, and we're still losing patients—13,000 deaths are expected in 2018. And so this is the scope of the problem, and we really are in urgent need of therapy. Selinexor is a drug that's an oral medication that has already been published in JCO this year in 79 patients, and the response rate was 21 percent, and that was in a blend of what we call quad- and penta-refractory patients and the dosing was either three out of four weeks or continuous.

So the purpose of this study that I presented today was really to extract out the truly unmet need so patients who had had all five drugs and were refractory to each drug class, so what we call penta-exposed triple-class refractory, and then study continuous dosing. So that was a patient population. It's important to recognize that the expected overall survival for this population can be as poor as 1.7 to three months. So this is who really need help.

So the study was done, and also the eligibility criteria were quite permissive. Renal function could be quite impaired, what we say creatinine clearance, many studies have 40 or 60. We allowed patients as low as 20. Neutrophil counts, only needed to get 1,000. Platelets could be as low as 50,000 if they had heavy marrow replacement. And I bring these up because sometimes relapsed/refractory studies cherry-pick patients so much that you get these great results, but then

when you transplant it to the real world it doesn't pan out. And so with this sick population we saw response rate of 26 percent, and the progression-free survival was 3.7 months.

Also important, the median overall survival was around 8.6 months and, as expected, the people that progressed did not do well. The median overall survival was only 1.7 months, but guess what? The patients who had minimal response and PRs, they had a median overall survival of 16 months, so that's very encouraging.

And what that tells us is that even if this therapy, if patients progressed on it, the toxicities—which I'll get to in a second—were not cumulative or debilitating. They were able to go on to other therapies and then extend their overall survival. So it was really, you can think of this drug as a bridge to the next therapy, which really we still need.

Andrew Schorr:
We haven't had that bridge before.

Dr. Chari:
Right. And each of these drugs incrementally provides this bridge.

And then the toxicities I think are important to go over, and there are basically four categories: gastrointestinal, fatigue, sodium being low and then blood counts. The blood counts are part and parcel of dealing with advanced myeloma. A lot of these patients had marrow replacement, and we could see that the likelihood of having low platelets correlated with what your platelets were when you went in to the study.

The other three require, as we do in oncology, really from the day a patient is diagnosed with cancer supportive care is essential and especially with this drug because there are toxicities, but the idea here is that these are patients whose disease is exploding. I didn't mention that, but it's important. In this study patients had a—from the day they signed consent and did their testing, screening tests to the day they enrolled, which was 12 days median, during that 12 days their myeloma numbers went up by 22 percent. So these are patients that are rapidly increasing.

So while—there was a lot of dose reductions and modifications for side effects, but the reason the doses started high is because we need to control the disease. If not, we're going to lose these patients. So the idea is start at this dose, get the disease under control and then de-escalate to manage the symptoms and then go forward.

And I think I would close by saying that the response rates are encouraging, and already combination studies are ongoing. My colleague, Dr. Gasparetto from Duke presented right after me and showed very exciting data for the combination of selinexor and daratumumab with response rates as high as 74 percent, when typically dara alone has a response rate of 25 percent. So I think this drug is an incremental addition and really fitting a niche which is currently not—has no other option.

And I really like to highlight one of our patients who still remains on single agent selinexor with dexamethasone (Decadron), and she's out over 60 weeks of therapy over a year, on oral medications, and she travels the world. And she had progressed right prior to this therapy on infusional 96-hour chemo, which causes profoundly low counts, so even though she progressed on that within two to three weeks these now on this therapy for over a year. So it's just a good example of how once you find that right dose and you can maintain it you can travel the world and not be chained to your doctor's office.

Andrew Schorr:
Wow. So as a myeloma specialist and researcher you must be encouraged that you're developing new options for even some of the sickest people.

Dr. Chari:
Absolutely. I mean, well, with all new novel agents you typically have to start with this population because first and foremost is safety. So we typically try to understand the safety profile of heavily treated patients, and as we get better and

we know what that is like these quickly move up earlier. And so this drug, selinexor, has also—this is potentially we're looking at accelerated approval because it's an unmet medical need. The FDA may give this special attention and get this approved quickly, but the pivotal study that would require confirmation of this is going to be a randomized study where in one to three lines of therapy everybody is going to get bortezomib and dex, and half will be assigned so the triplet selinexor as well.

And the study also allows crossover, so if you do get assigned to bortezomib dex you can roll over. And the reason I bring that up is when you go to combination settings the drug doesn't need to be given twice a week. You can give it once a week, so the toxicity profile improves. And so the idea is that can we hit this myeloma harder. And particularly to that point, one of the unmet medical needs in myeloma today is high-risk disease, and the way this drug works, which blocks proteins from being pumped out of the nucleus to the cytoplasm. So breaks like p53, which is universally bad in every disease, c-myc, other proteins that we know stimulate cancer growth, if you block the movement of those from where they're supposed to be then you can cause cell death. And so obviously tantalizing will be to see if this drug makes an impact in high-risk disease when it moves earlier.

Andrew Schorr:
Thank you so much, and thanks for your research that you're doing. I think for our audience this is really hopeful, and wouldn't it be great if some of these people who have been so sick with myeloma get to travel like that patient you talk about in New York City. Dr. Ajai Chari, thank you so much for being with us.

Dr. Chari:
Thank you. Good to be here.

Andrew Schorr:
Okay. Andrew Schorr here in San Diego as we cover myeloma. Watch this space as we continue to bring you more information for all the subtypes and individual situations of multiple myeloma. Remember, for you and your family, knowledge can be the best medicine of all.