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Favoring Novel-based Regimens Given Continuously versus Melphalan and Seeking Predictive Markers for the Efficacy of IMID-based Therapy: Ikaros and Cereblon

Raje: Hello, I am Noopur Raje. I am the director of the Center for Multiple Myeloma at Massachusetts General in Boston, and I am here at the 50th ASCO Meeting in Chicago. I am here with Keith Stewart, professor of medicine at the Mayo Clinic in Arizona. Thank you so much for being here Keith. It is a real pleasure.

Stewart: Thank you for inviting me.

Raje: You are presenting an interesting phase III ECOG trial with nearly 350 odd patients comparing melphalan-prednisone-thalidomide to melphalan-prednisone-lenalidomide, and I know it is being presented on Monday[1] so you are not going to give us the bottom line there, but if you can speak a little bit to that trial and some of IMiD-based trials which are ongoing in the upfront setting, that will be great.

Stewart: As we started our trial some years ago, it was to compare as you say the three-drug cocktail of melphalan-prednisone-thalidomide, but we did add thalidomide maintenance to the protocol versus the same regimen but with lenalidomide, so really a comparison of the two IMiD drugs.[1] The trial recruited 306 patients. The bottom line of the trial is that there was not much to differentiate the two regimens clinically. Response rates, depth of response, and progression-free and overall survival were somewhat similar for both regimens. Both regimens were relatively difficult for the patients to stay on for long periods of time. There was about 40% of the patients who had to discontinue therapy because of adverse events. What was different between the two arms was toxicity, and in fact, lenalidomide proved to be less toxic, and both of less grade 3 hematologic or less grade 3 non-hematologic toxicity, less DVT, less second primary malignancy, and I think importantly improved quality of life at the time when we measured which was 12 months after starting therapy. The conclusion of our trial was therapeutically equivalent but less toxic to use lenalidomide.

Raje: This brings up a really important point which you have alluded to Keith which is toxicity, and in the wake of the first trial, which was presented at ASH in the plenary session last year,[2] we saw and I think what we have learned over the last maybe 3 and 4 years in myeloma is continuing patients on therapy is really critical to trying to

increase both the response rate, increase the depth of the response, and then which ultimately translates into a progression-free survival benefit, and in that setting, they use lenalidomide-dexamethasone and compared it to an MP-based regimen, MPT. The difference between the len-dex based regimens were continuous versus 18 months of the treatment. Your thoughts on where we are going with MP and should we be switching more to len based, maybe minus the MP component?

Stewart: Since we started and somewhat completed this trial, the use of melphalan-based regimen in the United States has essentially stopped, and the reason stopped at the United States is because we have less toxicity and more potent therapies, and primary of among those are lenalidomide and bortezomib, and so the vast majority of the patients in the United States are receiving one of those two drugs. The first trial as you find out showed superiority for lenalidomide-dexamethasone compared to melphalan-prednisone-thalidomide which would suggest that even worldwide that lenalidomide would be more likely to be a better choice for the patients because of both prolonged progression-free survival and less toxicity.[2] So, I think life has moved on from the melphalan era, and we should embrace that.

Raje: Great. You have done a lot of work around mechanisms of actions, specifically with the IMiDs, and I think what has been really remarkable is the whole cereblon Ikaros story. Can you just put that data into some kind of perspective, and you have I believe a poster here as well in where you kind of use this as a predictive biomarker in the patients on pomalidomide.[3] Do you want to speak a little bit to cereblon Ikaros? What those transcription factors are doing and how they are modulated by the IMiDs?

Stewart: Yes. I think this is clinically relevant for the practicing physician, in that this came from a group in Japan[4] who pulled from cell's proteins which bound to these drugs, and one that they identified is this protein called cereblon, it gets its name because it was from the brain that was originally identified,[5,6] and they showed very clearly that you need this protein for the drugs to work, and they work by becoming part of the ubiquitination pathway.[4] They bind to cereblon, and they seem to turn on ubiquitination of certain proteins which are then targeted for destruction. One of those we should mention is called Ikaros,[7] and Ikaros is actually involved in normal B-cell development.[8,9] Interesting enough, when it is lost, it can contribute to some acute leukemia.[10,11,12] What we found is that in myeloma, and probably other cancers too, the presence of cereblon is absolutely required for these drugs to work.[13] It probably does work through this degradation of Ikaros, and if you measure either cereblon dominantly and maybe to a lesser degree of Ikaros in the tumor cell, you can predict whether the patient will respond to the drug or not, and you can also somewhat predict what their likely progression-free and overall survival would be.[3] Right now, there is no commercial test available to do this, but many companies are starting to work on this, both as a gene expression platform and also as an immunohistochemistry tool. So I think it will be something that over time might become part of the therapeutic workup with myeloma patients.

Raje: And that will allow us to guide treatment a little bit more rationally hopefully in the future so not everybody gets these drugs.

Stewart: And interesting enough, at diagnoses most patients who have fairly normal levels with these proteins and that makes sense because 90% of people respond. Where it becomes more important I think is in the later-stage patient where levels drop or there is a mutation which is not common, but if the levels drop, then only 30% of patients respond to these drugs in that situation, and knowing who to treat so that we maximize the efficacy of the drug and we benefit the patient, who need it and we can use other types of therapy for patients who are not going to respond, ultimately that is our goal.

Raje: I think the whole cereblon story, the fact that it is bearing out now clinically and it may be a potential biomarker in the future is really exciting. It will help us better categorize who should and should not be treated and also give us some insights into, we are now talking about continuous therapy but do we need to continue treatment forever in some patients and maybe protect a few patients from some of these drugs as well. One thing we have learned Keith I think over the last 2 and 3 years is duration of treatment, like we talked about a little earlier, is critical. The longer you stay on treatment the better. It is somewhat reflected in your ECOG study as well. Your thoughts on what we should be doing? How long should we be treating?

Stewart: Yes, so in our study, it does appear compared to the historic controls that did not use maintenance that our outcomes in terms of progression free and survival look a bit better, so confirming this notion that one should treat for longer than we used to. Nobody knows how long that should be. There is controversy over whether it should be 1 year or 3 years or indefinitely. Certainly in the first trial, I believe it was until progression, but in the post-transplant maintenance setting, we have tended to stop after a couple of years in our own practice. So that is certainly something that needs to be explored going forward, but my own experience is that many patients can tolerate 18 months to 2 years of therapy and then it becomes a little bit harder on them as we have tended to find that is about the right length of duration, but that is not evidence based, that is just practice based.

Raje: There is a little bit of treatment fatigue and to try and understand and I think address those issues we are beginning to do studies, especially in the maintenance field where we are looking at MRD, minimal residual disease. And I think going forward, some of those studies be very informative as to how long is enough as well.

Stewart: Yeah. The MRD testing has come along very quickly, both by DNA sequencing and by flow cytometry. I think it is really opening some new doors into how we explore and manage this disease. I personally use MRD testing as a decision point for whether to continue therapy sometimes.

Raje: That is great. So on that note, thank you so much for being here today, Keith. That was very helpful, very informative. Thanks so much.

Stewart: Thank you for inviting me.

References:

1. Stewart AK, Jacobus SJ, Fonseca R, et al. E1A06: A phase III trial comparing melphalan, prednisone, and thalidomide (MPT) versus melphalan, prednisone, and lenalidomide (MPR) in newly diagnosed multiple myeloma (MM). *J Clin Oncol*. 2014;32:5s (suppl; abstr 8511).[Link to abstract]
2. Facon T, Dimopoulos MA, Dispenzieri A, et al. Initial Phase 3 Results of The First (Frontline Investigation of Lenalidomide + Dexamethasone Versus Standard Thalidomide) Trial (MM-020/IFM 07 01) In Newly Diagnosed Multiple Myeloma (NDMM) Patients (Pts) Ineligible For Stem Cell Transplant (SCT). *Blood [ASH Annual Meeting Abstracts]*. 2013;122(21):Abstract 2. [Link to abstract]
3. Zhu YX, Braggio E, Shi C-X, et al. Ikaros Expression Levels to Predict Response and Survival Following Pomalidomide and Dexamethasone in Multiple Myeloma. *J Clin Oncol*. 2014;32:5s (suppl;abstr 8540). [Link to abstract]
4. Ito T, Ando H, Suzuki T, et al. Identification of a primary target of thalidomide teratogenicity. *Science*. 2010;327(5971):1345-1350. [PubMed]
5. Higgins JJ, Pucilowska J, Lombardi RQ, et al. A mutation in a novel ATP-dependent Lon protease gene in a kindred with mild mental retardation. *Neurology*. 2004;63(10):1927-1931. [PubMed/Full Article]
6. Jo S, Lee KH, Song S, et al. Identification and functional characterization of cereblon as a binding protein for large-conductance calcium-activated potassium channel in rat brain. *J Neurochem*. 2005;94(5):1212-1224. [PubMed]
7. Lu G, Middleton RE, Sun H, et al. The myeloma drug lenalidomide promotes the cereblon-dependent destruction of Ikaros proteins. *Science*. 2014;343(6168):305-309. [PubMed]
8. Georgopoulos K, Bigby M, Wang JH, et al. The Ikaros gene is required for the development of all lymphoid lineages. *Cell*. 1994;79(1):143-156. [PubMed]
9. Schwickert TA, Tagoh H, Gültekin S, et al. Stage-specific control of early B cell development by the transcription factor Ikaros. *Nat Immunol*. 2014;15(3):283-293. [PubMed]
10. Sun L, Heerema N, Crotty L, et al. Expression of dominant-negative and mutant isoforms of the antileukemic transcription factor Ikaros in infant acute lymphoblastic leukemia. *Proc Natl Acad Sci U S A*. 1999;96(2):680-685. [PubMed/Full Article]
11. Mullighan CG, Miller CB, Radtke I, et al. BCR-ABL1 lymphoblastic leukaemia is characterized by the deletion of Ikaros. *Nature*. 2008;453(7191):110-114. [PubMed]

12. Pang SH, Carotta S, Nutt SL. Transcriptional Control of Pre-B Cell Development and Leukemia Prevention. *Curr Top Microbiol Immunol*. 2014 May 16.[Epub ahead of print] PubMed PMID: 24831348. [PubMed]
13. Zhu YX, Braggio E, Shi CX, et al. Cereblon expression is required for the antimyeloma activity of lenalidomide and pomalidomide. *Blood*. 2011;118(18):4771-4779. [PubMed/Full Article]