What's New in Multiple Myeloma Management?

Multiple myeloma is diagnosed in over 100,000 patients each year worldwide. The FDA recently granted accelerated approval to Teclistamab, the first bispecific B-cell maturation (BCMA)-directed CD3 T-cell engager. The therapeutic armamentarium for myeloma now includes alkylating agents, corticosteroids, deacetylase inhibitors, immunomodulatory agents, monoclonal antibodies, and proteasome inhibitors and continues to evolve. We are talking to Dr. Ravi Vij to explore myeloma therapies under development that promise to bring us closer to the cure of this plasma cell cancer.

Full Transcript:

Shweta Mishra: Hello and welcome to CureTalks. Today we are discussing new developments that happened in the world of myeloma management in the past few years. I'm Shweta Mishra: and we have with us today, Dr. Ravi Vij, Professor of Medicine in the Division of Medical Oncology at Washington University, School of Medicine, and Founder of the non-profit organization- mycancerhaven.org. Joining Dr. Vij on the panel is Jack Aiello, a leading myeloma patient advocate who is involved with several cancer advocacy organizations. I welcome you both, Dr. Vij, and Jack, to the panel today. Thank you for joining.

Dr. Ravi Vij: Thank you.

Shweta Mishra: Thank you. To start with, I want to mention that the median survival for myeloma patients has now increased to about 8 to 10 years compared to only about three years, right? That they had about two decades ago and the agents and treatments that FDA has approved over a decade has contributed significantly to this improved outcomes, right? So, could you please briefly share some highlights of the new developments that happened in the field of myeloma management in the past few years?

Dr. Ravi Vij: Yeah, I think the management of multiple myeloma has been revolutionized in this millennium. First decade, we saw the advent of drugs like proteasome inhibitors, immunomodulatory drugs that change the landscape of treatment but six or seven years ago, we started seeing monoclonal antibodies appear daratumumab, emplicity and these further improve outcomes for patients and now we are entering a new era of immunotherapy and I think the best is yet to come and we only started to see the beginnings of the next major, I would say leap in outcomes for patients with multiple myeloma and the main thing that I think people are most excited about right now are CAR-T cells bispecific antibodies. But there are other advances that are also happening concurrently including drugs like Venetoclax for patients who have the 11-14 translocations, they will also be coming to market in the not-too-distant future.

Shweta Mishra: Thank you. Thank you for that rundown, Dr. Vij, I know Jack will have more specific questions on this to you but I was recently reading out and found that a group of chemists, I believe from MIT, they have designed a nanoparticle, which kind of looks like a bottle brush and they can load multiple cancer drugs on it and deliver combination of drugs to the myeloma cells. So, it's also fascinating, could you talk a bit about how nanoparticles work to treat cancer and how do they solve the limitations of conventional cancer treatments and also talk about a bit about the progress that has happened in the field of nanotechnology for cancer?

Dr. Ravi Vij: Yeah, I think that nanotechnology has great potential in drug delivery. The fact is that nano particles are particles that are smaller than the breadth of a human hair. And these are the agents for drug delivery. We have actually some nanoparticle related drugs already on the market, for example, liposomal doxorubicin, which is actually approved for Multiple myeloma, is actually a nanoparticle-based therapy. So, nanoparticle-based therapies happen and there are number of other liposomal products that are used in different cancers. But yes, now the field is moving towards even more remarkable advances and the use of

these because you can actually quote, these particles with targeted agents and they can then go and deliver the agent specifically to the target of interest and have little in the way of off target effects. So, nanotechnology, I think is something that holds great promise. At Washington University we actually had for 5 years a NIH funded grant looking at nanotechnology for treatment of multiple myeloma. And a lot of preclinical have been made and hopefully these will translate into therapeutics in the years to come.

Shweta Mishra: Right. Thank you. And before I pass it on to Jack, I want to talk to you about the non-profit mycancerhaven.org that you started, Dr. Vij. Could you talk about its objective a little bit and how it will help patients and physicians advance myeloma care?

Dr. Ravi Vij: Yes. So, thank you for asking. So, this is a not-for-profit that I actually established in 2017. The mission of the not-for-profit is to provide a custom design curated and moderated platform where not only cancer patients, but cancer focused experts, researchers and organizations can come and create cancer specific ecosystems to enable dissemination of information, education and research initiatives. So, it is meant to bring all the stakeholders there together. We have started in myeloma in January this year. I'm very grateful to Jack who has been very helpful in getting this effort off the ground as well. And what we have on the platform are educational tools, including videos, we have physician experts and other experts that have started producing blogs specifically directed to a patient audience. There are other platforms certainly out there, but they don't usually have a cancer focused and some of them don't have the ability then to provide wetted information, for that reason, we think this would be a unique platform. We also are able to provide up to the minute curative today feed and newsfeed. Patients have the ability to form groups and also message each other. We engage the patients with educational quizzes and actually what the other important initiative is to get the patient's perspective, researchers have questions, we can pose them to the patient community. We also are going to be opening it up to Leukaemia and Lymphoma this month and hopefully months to come to additional cancer types as well. So, thank you for allowing me to talk to the audience about this platform and it is accessible right now only in the United States at mycancerhaven.org website.

Shweta Mishra: Thank you. Thank you for sharing that with us, Dr. Vij good to know information about it and I guess with that, I will now pass it on to Jack, to take the discussion forward. Jack, please, take over.

Jack Aiello: Thanks Shweta and Dr. Vij thanks so much for being available for this talk. I was diagnosed more than 28 years ago and it's just amazing to see the continual evolvement of treatment and the increase seemingly in treatments for myeloma over the past few years. For example, if I'm a newly diagnosed patient I'm going to get what's called induction therapy. But these days if I'm getting educated, I'm hearing that there are for transplant eligible patients, three drug regimens or four drug regimens and there are different regimens for non-transplant eligible patients for induction. Can you talk about that? And how do you decide even at induction what treatment to take?

Dr. Ravi Vij: Yeah, that is a very good question and you're right I think what we are seeing is that the transition in the transplant eligible patient from three drug regimens to four drug regimens is ongoing. In the community, three drug regimens are still very commonly being used but at least in academia we have transitioned to four drug regimens based on the observation from several clinical trials that the depth of response including minimal residual disease negativity is much higher with four drugs, including the antibody daratumumab or isatuximab and with that we anticipate that we will in the years to come be able to show a much _____ time of disease control and hopefully also longer lifespan for our patients. Yes, that it will take years to demonstrate that, so either we can rely on what we call surrogate markers that have in the past with stared the test of time and anticipate that we are doing good by making this transition already. As regards, those that are not transplant eligible there at the moment, three drug regimens are the standard of care but there too we are anticipating trials to read out very much in the near future where four drug regimens may surpass the three drug regimens of today. Two, three drug regimens that are probably most commonly used today are daratumumab with bortezomib and daratumumab with revlimid and dexamethasone and lenalidomide with bortezomib and dexamethasone. There's no consensus on which is the best, but I think that more and more people are definitely using three drug regimens.

Jack Aiello: The unfortunate part is that most patients or fortunately will do well with any of these regimens. But at some point, they probably will relapse, their treatment stops working even if they're put on maintenance treatment, which is quite common. So, for those relapse or refractory patients, what factors do you consider when making the next treatment decision since there are even more treatments available at the relapsed/refractory stage?

Dr. Ravi Vij: That is very true. So, the fact is that it is actually a good problem to have that we have an abundance of riches. We have a lot of different options to choose from and once again, if there is a little consensus sometimes in front line therapy, the consensus in little lines of therapy is even less so, and the treatment of myeloma is as much art as it is science, the use of three drug regimens, again in little lines of therapy, second, third line has now replaced two drug regimens that were used in the past. After a number of trials, have shown that three drug regimens, outperform two drug regimens. In the second line displays we have the ability to give daratumumab based three drug regimens – daratumumab with carfilzomib and dexamethasone, daratumumab, velcade and dexamethasone, daratumumab with revlimid and dexamethasone and in the later line of therapy also daratumumab with pomalidomide and dexamethasone. I think the daratumumab based regimens have been the mainstay for second-line therapy for the last few years because patients that today are seeking second-line therapy are not, what we call Quad refractory. They are not usually exposed or refractory to daratumumab because they started their cancer journey in an era when daratumumab was not commonly used in front line. So, which of these daratumumab based regimens to use is very much dependent on the physician but also on a number of patient characteristics like what they have had in a prior line of therapy, what their comorbidities are, what their performance status is, what their social situation is like, so number of factors go into this decision making. Also, in somewhat old and frail patients, sometimes two drug regimens are still used as you get into a later line of therapy you see once again, what you used in your second line, and you try to come up with a new combination for third line or frequent. Obviously, when you get into much later lines of therapy like fifth line and beyond, we are now seeing an abundance of new options of being available, you had for the typical class refractory patients Selinexor that was marketed several years ago, it is given not as a dual therapy these days but as part of three drug regimens often, and BCMA based treatments are really where the focus has shifted in that line of therapy now. We now have two CAR-T cells, that are approved. They have been in such a short supply, but the good thing is some of the production constraints are now seemingly easing. So hopefully, this will become available to more patients in the very near future. And then in the last few months we've seen the approval of the first by specific to BCMA teclistamab, which offers patients ready off-the-shelf availability of therapy which also offers patients the potential to be treated closer to their community colleges and not necessarily in large academic centres. Once the setup in the community is complete to manage CRS and some neurological toxicity. So, a long-winded answer to your simple question. But unfortunately, there is not a simple answer to that question.

Jack Aiello: Well, that's really important what you're saying in terms of having community oncologist able to give these new treatments because we need to reach as many myeloma patients as possible. You mentioned earlier, in one of your answers to Shweta about the two new exciting areas, CAR-T therapy, we have a couple of FDA-approved CAR-T Therapies in the US and bispecifics, we already have one by specific approved in the US, as well as two approved for accelerated approval. So, and then many more of these CAR-Ts and bispecifics in clinical trials. So maybe you can just for the new patient give a quick summary of what CAR-T and bispecifics are? And then what did we learn from the recent December's ASH American Society of Hematology meeting about these treatments going forward?

Dr. Ravi Vij: So, CAR-T cells are the state-of-the-art technology whereby we can modify a person's immune system to recognize the cancer. What is done, is we collect the immune cells through a process called pheresis. These are then shipped to a manufacturer and there are expanded and genetically modified to recognize the cancer. It takes anywhere from four plus weeks to get the processing of these complete today. Once these are ready to be shipped back then patients are given some outpatient chemotherapy generally and this is not of the intensity of stem cell transplantation and thereafter, they're admitted for the infusion of the CAR-T cells, which go in less like a stem cell infusion, just like any blood product infusion and these cells then multiply in the body to recognize the cancer and depending on the type of CAR-T cell being used.

Anywhere from 24 to 48, or as long as seven days later patients, drop off an entity called cytokine release syndrome wherein when these cells are recognizing their target, they secrete chemicals that make the body run a fever. Sometimes, patients end up on the oxygen and drop of their blood pressure. It is rare to end up in an ICU setting. But these are also associated in some cases with periods of confusion, which can be real distressing to the family members. But in nearly all cases, this is transitory and resolves within a few days. And what we've seen is with this what we call one and done approach, anywhere from one to two plus years of good disease control. So, patients don't need to be tied up to treatment for extended periods of time and this is in little lines of therapy when patients have progressed to four prior regimens. It is anticipated that each movement to earlier lines of treatment that the value proposition would be much greater. As regards to bispecifics, those are, as we had said off-the-shelf therapies. So, whereas there is a lag period to get a CAR-T because of insurance approval, production issues and some patients whose disease is progressing rapidly may not be able to wait long enough, a bispecific is available very quickly for administration to the patients. And one that is currently approved called teclistamab requires three ramp up doses and at during which once again, some CRS and rarely neurological toxicity may be encountered but much less intense that seen with a CAR-T and once the patient has received the first full therapeutic dose, then patients, literally do not have any other problems thereafter and they can be managed as an outpatient with at the moment teclistamab weekly injections. This is something that again provides long benefit to a year and a half on an average and some patients even more. With bispecifics as with CAR_T cells, what we see is a very rapid decline in disease burden in those patients that are going to respond. For those that don't have as good a response we see relatively rapid recurrence, but good thing is for the majority where the disease goes into a deep remission, the remission periods are very long.

Jack Aiello: So, just to remind folks CAR-Ts are kind of a one in done, I get it and then medically I'm not on treatment anymore until perhaps the myeloma scene is coming back versus bispecifics, are infusions that are given every couple of weeks, let's say and these continue until what's called progression or the disease coming back. Is that correct?

Dr. Ravi Vij: That is very true.

Jack Aiello: And do these all work in the same ways? Do they find the myeloma cell in the same way? And can I use both of these treatments?

Dr. Ravi Vij: That's a very good and an excellent question. So, the fact is that as far as the BCMA based treatments go I think quite a few patients are going to get more than one different modality of treatment directed to BCMA. What the optimal method of sequencing still remains to be worked out. But the early data suggests that once you have had CAR-T un-responded, then going with a bispecific offers a fairly good chance of response. On the other hand, if you get a bispecific and you progress, your disease progresses on a by specific and you go to a CAR-T soon afterwards, the CAR-T's efficacy is somewhat limited, but if there is a gap between the period of exposure to the bispecific and CAR-T infusion, longer the Gap, the longer the chances of a CAR-T helping you. The good thing is as you hinted about do these all work in the same way that we have actually new targets that we have identified that are also the subject of bispecific and CAR-T therapy GPRC5D, Talquetamab, a bispecific to this has now been put before the FDA and if all goes well may actually be the second bispecific to myeloma to be approved sometime later this year and the CAR-Ts to GPRC5D have been presented. Both of these modalities once again work in the majority of patients and what is very exciting is it work even in patients whose disease has progressed after exposure to a BCMA based treatment. So, I think that we have now got not only BCMAs, but we have other targets FcRH5 is another target. Cevostamab a bispecific antibody to FcRH5 receptor has also shown very robust activity. But we however need to be cognizant of the fact that bispecifics is and there are some other side effects that may be needing to be tackled with GPRC5D. The issue with skin and nail toxicity has been demonstrated and then an entry called dysgeusia where patients are not able to swallow food and lose weight can be an issue in a proportion of patients. Also as a class BCMA bispecifics seem to also have higher rate of infections and we are only now starting to see some of the infections emerge that we usually have seen in the post allogenic transplant space. CMV, Adenovirus infection, hemolytic anemia infections, these are things that we don't usually see in a non-allogenic transplant population, but we have started

seeing them in some patients with bispecific which has brought up the question on that should bispecific be given to progression. They do a great job in a lot of patience, and they are in MRD negative complete remission within a few months of starting therapy. So, some postulating that we may need to go back to the old paradigm where you treat, you give a treatment for internal and re-intervene. So, we'll have to see how this story unfolds.

Jack Aiello: So, one of the keys as you were mentioning is developing treatments that pick these targets. You mentioned BCMA, that's one of the antigens found mostly on myeloma cells but not elsewhere versus where there's a different target, like the GPR5D or whatever that was, that might be found on other cells, and therefore, might lead to different types of side effects. Is that correct?

Dr. Ravi Vij: Yes, it is very good. GPRC5D expression on skin, nail and the epithelium of the tongue. Now, BCMA is very specific to the myeloma cell, but also some off target expression in the basal ganglia of the brain has been demonstrated and so one needs to be a little vigilant about it's use and look out for those parkinsonian symptoms that have been reported in a few patients in clinical trials.

Jack Aiello: Okay. You mentioned MRD earlier, which stands for either Minimum Residual Disease, or Measurable Residual Disease. But can you explain what that is, and should patient be requesting this MRD test and do you use it to help figure out what treatment might be given next?

Dr. Ravi Vij: Sure. So, as you said, Minimal Residual Disease, now more commonly called Measurable Residue Disease is a state-of-the-art technology that allows you to detect 1 cell abnormal in a hundred thousand per 1 cell abnormal in 1 million. To put in perspective, when we look at cells under a microscope, which has been the conventional definition of a complete remission, you count 100 cells and see if you see any cancer cells. So, these technologies are able to detect cancer at a much lower level than has been previously feasible. There are different technologies, flowcytometry or next-gen sequencing-based technologies that are being employed. The fact is indisputable that these tests are predictive of long-term outcomes. Patients who achieve MRD negativity too far, better than those who are MRD positive after a finite period of treatment. What we still lack is proof that for patients who are MRD positive giving them more treatment to achieve MRD negativity changes their long-term outcome. And this is being studied in clinical trials, however, already quite a few physicians, there is no consensus on this field again feel that, especially for patients with high-risk disease, it may be worthwhile giving additional treatment to try to deepen the response because high risk disease patients unfortunately do to have shorter periods of remission. And these are usually the patients that have genetic abnormalities like p53 deletion, 44p, 14-16, 14-20 translocation. So, for them may be this is already something that we can avail of. We also know in clinical trials, we are seeing some early trials, looking at CAR-T being given for patients who are MRD positive return them to MRD negativity and early data from such studies suggest that is perhaps some superiority to that approach. The Physicians are still not lacking a census on whether MRD is ready for primetime clinical use in all patients. There are some physicians who are already making decisions about when to discontinue maintenance therapy based on MRD negative status. The fact is that this is being addressed again in clinical trials. However, it will be several years before we have firm results from prospective clinical trials to answer this question. But we already have often patients who are having side effects and they are on one hand scared to stop the treatment. On the other hand, the quality of life is suffering because of the maintenance therapy they are on. So again, without any definitive proof, I think that in such a situation checking MRD and two successive points, six months to a year apart, perhaps and stopping if you are MRD negative may offer the best solution for those patients. And others are using MRD to monitor patients on a longitudinal basis. When you go from MRD negativity to MRD positivity, should you intervene or change treatment, this again, is something that there is no proof right now, is something that will make a difference, long term in a patient's care. But these are the questions that are needing to be answered in the trials, in the years to come.

Jack Aiello: So, it's interesting more treatment options, both for induction and for relapse patients lead to more questions being asked and need to be answered, but it's exciting, I appreciate your answers and I'll turn it back over to Shweta.

Shweta Mishra: Thank you. Thank you, Jack. Dr. Vij it was great listening to both of you. Dr. Vij, before we conclude the talk today, it will be great if you could talk a bit about your vision. What is your vision for improving Myeloma treatment for the next decade?

Dr. Ravi Vij: I think that we as I said are in the transformational age for multiple myeloma patients, as these new immune based therapies are coming out. We are now going to see these moving into earlier lines of treatment but already probably in the next year or so going to have the ability to give CAR-T cells in second line and third line. The use of bispecifics in those lines will follow. Ultimately, these are going to be moving into first line treatment. The question is, will we start seeing more patients being cured? When I say more patients, we certainly do have patients that are already cured of myeloma, patients who've been in remission but two decades or more. We have living proof of such individuals and I think that what we will see hopefully, is a greater proportion of patients now being cured. Now, whether these treatments display what is still going to be for most people, the standard of care, if possible, which is stem cell transplant, or they're going to be used in conjunction with stem cell transplant, to achieve these cures remains to be seen. But I think that immunotherapy was great potential and who knows what else will come down the pike in the years to come.

Shweta Mishra: Right, thank you. Thank you, Dr. Vij, thanks for all the information you shared. Great session and we learnt a lot. Jack, thank you for guiding the panel with your insightful questions and we will make this talk available on curetalks.com very soon. So, until we meet next, thank you, everyone and have a great time.

Thank you very much.