Managing Myeloma

Bcl-2 Inhibitors, Antibody Drug Conjugates and SINEs

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My name is Shaji Kumar. I am a Professor of Medicine at Mayo Clinic in Rochester, Minnesota. I am here live at the annual American Society of Hematology meeting in San Diego. What I would like to do today is discuss four abstracts from this meeting that represent some exciting new drugs for patients with multiple myeloma. The first one I would like to talk about are two abstracts that deal with venetoclax, a new drug that is being investigated in treatment of relapsed multiple myeloma. The Bcl-2 family of proteins is involved in preventing the cells from dying, and these are often responsible for cells not responding to chemotherapy and other treatment agents. Venetoclax is a selective inhibitor of the Bcl-2 molecule, and in the laboratory, it clearly shows efficacy against myeloma cells, both by itself and in combination with other drugs such as bortezomib and dexamethasone. There were two clinical trials that were designed based on the initial encouraging results that were seen in the laboratory. The first one looked at venetoclax as a single agent, 66 patients were enrolled into a phase 1 trial. The patients had to have at least one prior line of therapy and should have had relapsed multiple myeloma. What we found in the study was that the drug was very well tolerated. Adverse events were primarily related to hematological toxicities and could be managed with dose modifications. The second common group of side effects that we saw were gastrointestinal toxicities; primarily nausea, vomiting, and diarrhea. None of these toxicities were grade 3 or 4 and they were easily managed, again with dose modifications and symptomatic management of the side effects. None of these toxicities were longstanding. There were no dose-limiting toxicities and no patients went off study because of the side effects related to the medication. In terms of efficacy, we saw a 20% overall response rate including a 15% very good partial response rate among the 66 patients who were enrolled in the study. The median duration of response was about 10 months and the median time to progression was about 2.6 months in this trial. What was particularly interesting from this Phase 1 study was the response that we saw in a subgroup of patients with translocation t(11;14). Now, in the laboratory, we already knew that patients with t(11;14) translocation had high levels of Bcl-2 and low levels of Bcl-xL, another member of the Bcl-2 family protein which prevents cells from going into apoptosis. So, these t(11;14) patients had a 40% overall response rate to the single-agent venetoclax, which was quite striking. What was even more interesting was that among the subgroup of patients who were 11;14, which were about 30 in number, the patients who actually had high levels of Bcl-2 and low levels of Bcl-xL by PCR on the tumor samples, had an 85% response rate. This raises the possibility that we could now have a drug in myeloma that is selected based on a particular biomarker. Even more important is the fact that this efficacy was with single-agent venetoclax and opens up the possibility of adding this drug to other drugs that we currently use in the clinic. So, along those lines, in particular the combination with bortezomib is of great interest. Now, in the laboratory, we have seen that when you combine venetoclax with bortezomib, there is a significant enhancement of the ability to destroy myeloma cells. Bortezomib can actually decrease the levels of MCL-1 which is another member of the of Bcl-2

family of anti-apoptotic proteins. So, by simultaneously decreasing the MCL-1 levels by using the bortezomib and decreasing the Bcl-2 levels by using venetoclax, we are able to cause substantial death among myeloma cells. So, the Phase 1 trial looked at escalating dosage of venetoclax and bortezomib in patients with relapsed/refractory multiple myeloma. What we saw in the study was that the adverse event profile was quite favorable. The most common side effects we saw were again related to hematological toxicities such as neutropenia and thrombocytopenia. We also saw some gastrointestinal toxicity similar to what we saw with venetoclax alone. We also saw some toxicities which are ascribed to the bortezomib such as peripheral neuropathy. Overall, the toxicity profile was very manageable with dose modifications and symptomatic therapy. In terms of efficacy, the overall response rate was almost 68%. In particular, if you look at the subgroup of patients who had one to three prior lines of therapy and were not refractory to bortezomib, the response rate was over 90% in that group of patients. Now, when you think about the data in the similar groups of patients who were treated with bortezomib and dexamethasone, what we saw here was substantially higher than what you would have expected from the control group of recently concluded phase 3 trials. So, it is clear in the clinic that we are seeing findings that are consistent with what we saw in the laboratory. The median duration of response was almost 10 months and the median progression-free survival was in excess of 12 months. Again, suggesting that the responses that we saw with this combination are fairly durable. Now, this combination raises two possibilities: that venetoclax can be successfully combined with the proteasome inhibitors to have significant efficacy in this disease, but it also raises the possibility that we could potentially combine venetoclax with the variety of other myeloma drugs that are currently being used in the clinic, again increasing the options for patients with multiple myeloma. So, in summary, we are looking at a very exciting drug that could translate to a biomarker-driven therapy in multiple myeloma and one that could actually be combined with the variety of the drugs to make those drugs work even better.

Now, the third abstract that I would like to talk about today is a drug called GSK2857916. Now, this is an exciting drug. It is a monoclonal antibody against the protein called BCMA or a B-cell maturation agent that is present on the surface of plasma cells. Now, it is fairly unique in terms of its expression on the myeloma cells or in general plasma cells, so it can be categorized as a fairly targeted therapy for the myeloma cells. The antibody is actually conjugated to a toxin called monomethyl auristatin F, and when patients receive therapy the antibody allows these drugs to be directed toward the myeloma cells. The antibody binds to the myeloma cell and the drug conjugate is then released and internalized into the myeloma cell, which then undergoes cell death. What was seen in the clinical trial, we just have a relatively small Phase 1 study looking at increasing dosage of the GSK drug clearly demonstrated that it can be efficacious, so one patient with a good partial response and three patients with a partial response and one patient with a minor response. Now, considering how relapsed and refractory these patients were going into the trial, these responses are very encouraging and the trial is proceeding to larger trials. Now, the adverse event profile was very favorable as well. The majority of the side effects that were seen were related to the infusion itself; chills and fevers are fairly common. In particular, there were some eye symptoms which we believe is related to the toxin that is bound to the antibody. So, again, there is a lot of interest in immunotherapy in myeloma. There are exciting monoclonal antibodies that have been approved for treatment of myeloma such as daratumumab. However, this particular drug raises the possibility of even further enhancing the antibody therapy by conjugating that with a toxin which we believe will have a more effective way of reducing the tumor cells.

The last drug that I want to talk about is selinexor. There are two studies being presented at this meeting with selinexor and selinexor combination. The first one I would like to talk about is selinexor being used as a single agent or in combination with dexamethasone. Now, the way selinexor works is it is a nuclear export protein inhibitor. So, a lot of the proteins that are being transferred outside of the nucleus can be inhibited by inhibiting this transporter protein using selinexor and what has been seen in the laboratory is that selinexor can kill a wide variety of cancer cells by inhibiting a basic mechanism. The toxicities that were seen in this Phase 1 study were predominantly hematological toxicity. So, we saw thrombocytopenia as well as neutropenia, and there was also non-hematological toxicity, predominantly GI toxicity like nausea, anorexia, and vomiting as well as some weight loss. Now, all these toxicities could be managed with dose modifications or with symptomatic management, and most patients will manage to stay on therapy and the most common reason why patients went off study was disease progression. The overall response rate in this study was about 21% including a very good partial response of 5%, and the overall survival was 9.3 months with a progression-free survival of about 2.1 months. The responses when they happened were reasonably durable with the median duration of response of about 5 months, which is important because these are a group of patients who are very refractory. Out of the 79 patients enrolled in the study, 48 patients were refractory to all four drugs: lenalidomide, pomalidomide, bortezomib, and carfilzomib. Furthermore, 31 patients were penta-refractory, meaning refractory to all these four drugs and also to daratumumab. So, these are patients who really do not have a lot of treatment options, and this drug clearly demonstrates a clinical benefit. This drug has also been combined with carfilzomib and bortezomib and both of those studies are also looking very encouraging at this point.