Managing Myeloma

Abstract 139

Primary Results from the Phase 3 Tourmaline-AL1 Trial of Ixazomib-Dexamethasone Versus Physician's Choice of Therapy in Patients with Relapsed/Refractory Primary Systemic AL Amyloidosis

Shaji K. Kumar, MD
Professor of Medicine
Medical Director
Clinical Research Office
Mayo Clinic Cancer Center
Rochester, Minnesota

Welcome to *Managing Myeloma*. I'm Dr. Shaji Kumar and I'm live at the 61st ASH conference in Orlando, Florida. Today I will be reviewing the results of the oral presentation titled, "Primary Results from the Phase 3 Tourmaline-AL1 Trial of Ixazomib-Dexamethasone Versus Physician's Choice of Therapy in Patients with Relapsed/Refractory Primary Systemic AL Amyloidosis."

Light-chain amyloidosis, or primary systemic amyloidosis, is a plasma cell disorder that is associated with significant organ dysfunction secondary to deposition of light-chain amyloid protein in a variety of different organs. In contrast to multiple myeloma, light-chain amyloidosis often is associated with a relatively low level of plasma cell burden. But the free light chains that are being produced has the ability to be converted into amyloid fibrils, which then deposit in different organs, creating the clinical picture that is consistent with multi-organ dysfunction seen in this disease. It can be a fairly challenging disease to treat, primarily because there are no approved therapies.

The treatments that we use in the clinic for treating light-chain amyloidosis have mostly been borrowed from those that are used for treating multiple myeloma. The primary goal in the treatment of light-chain amyloidosis is fairly similar to what we do in myeloma, which is trying to eradicate, or at least significantly decrease, the tumor burden or the burden of plasma cells. Unlike myeloma where patients can derive long-term benefit without a complete eradication or even without achieving a very low level of tumor cells, in amyloidosis it is imperative that we achieve a low level of tumor burden because even small levels of free light chain can continue to cause organ dysfunction. The current therapies that we use in this disease include the combinations of melphalan and dexamethasone or bortezomib with cyclophosphamide and dexamethasone, and in patients who are eligible to undergo autologous stem cell transplant, that is also used.

Ixazomib is a new oral proteasome inhibitor that has been demonstrated to be active in patients with multiple myeloma, both alone and in combination with dexamethasone, or in combination with immunomodulatory drugs like lenalidomide or pomalidomide. It has also been shown to be effective in combination with cyclophosphamide and other alkylating agents in patients with relapsed myeloma. Ixazomib has been studied in the context of light-chain amyloidosis in a small phase 2 study where it was shown to be effective in inducing hematologic response that then translated to organ response. Unlike multiple myeloma, just obtaining a hematologic response is insufficient in amyloidosis, and what is clinically relevant is the ability to obtain an

organ response that is an improvement in the organ function. At the minimum, we want to be able to get to a hematologic response that will translate to a slowing down of the organ dysfunction, and preferably an improvement in the dysfunction over time. The difficulty in assessing the response to therapy in amyloidosis is that the hematologic response, even though it can happen early on, the organ response can take several months to maybe even up to a year to happen. Thus, making it difficult to read out that endpoint in the context of clinical trials.

Another difficulty in the setting of amyloidosis is the fact that the degree of hematologic response does not always correlate well with the organ response, even though in the majority of the patients who achieve a complete response or a very good partial response, in terms of hematologic response, typically do achieve some degree of organ improvement. So, this particular clinical trial was designed to look at the role of ixazomib and dexamethasone in patients with light-chain amyloidosis who have previously received therapy. And the trial was designed to look at what we call a physician's choice, which is essentially randomization between getting ixazomib-dexamethasone or two or three different regimens that have been allowed within this study that the treating physician can choose from for the patients who are randomized to the control arm.

Overall, 168 patients were randomized in this clinical trial, 85 to the ixazomib-dexamethasone and 83 patients to physician's choice. When you look at these patient groups, they are fairly balanced with maybe a slight increase in the rate of cardiac involvement in the ixazomib group. When you look at the prior therapies, nearly half of the patients had received bortezomib and nearly half of the patients had received transplant, and they were fairly evenly distributed between the two groups. The median time from diagnosis was a little over a year in both these groups.

When you look at the response rate for the therapy, the overall hematologic response was comparable between the ixazomib-dexamethasone and the physician's choice, with approximately half of the patients getting hematological response. However, when you start looking at the deeper responses, nearly 26% had a complete response with ixazomib-dexamethasone compared to 18% for the control arm. Furthermore, when you start looking at the organ response, nearly three times as many people in the ixazomib-dexamethasone achieve an organ response compared to the control arm where only 11% of the patients actually had an organ response; and these findings were consistent within those patients with cardiac involvement – where we look for cardiac response – and in those with renal involvement.

A variety of other endpoints were also evaluated in this study. One of them that is clinically highly relevant is the time to vital organ deterioration, which essentially refers to either cardiac or renal worsening. And this was significantly better for the ixazomib-dexamethasone compared to the physician's choice where a higher proportion of patients had deterioration of this organ function in a shorter timeframe compared to getting ixazomib and dexamethasone.

The overall survival was not assumable in either of these groups; however, the trend was in favor of the ixazomib-dexamethasone arm. Similarly, the time to subsequent therapy was also much better for the ixazomib-dexamethasone compared to the physician's choice. The duration of response was also superior with the ixazomib and dexamethasone. And the time to treatment failure was twice as long in the ixazomib group compared to the physician's choice, also suggesting that there's a benefit to using ixazomib and dexamethasone.

The median duration that patients stayed on therapy was significantly longer in the ixazomib-dexamethasone compared to the physician's choice.

When you look at the overall toxicity profile, it was fairly comparable between the two groups, suggesting that the ixazomib-dexamethasone did not add any additional toxicity compared to what was used with the physician's choice. However, there were more patients who discontinued therapy with the ixazomib-dexamethasone, and there was also an increase in the serious adverse events in the patients receiving ixazomib-dexamethasone.

When you look at the side-effect profile, it is clear that a trend towards more infections in patients receiving Ixazomib and dexamethasone. There were also more GI side effects, especially nausea, in patients receiving ixazomib and dexamethasone.

Now, the findings on this trial clearly demonstrate that patients can benefit from the ixazomib used in combination with dexamethasone; however, the trial did fail to meet the primary endpoint of the hematologic response, which unfortunately means that this drug will not be approved at this point for use in light-chain amyloidosis. However, there is continuing effort to look at other novel combinations with this drug, given the fact that we do see the other endpoints being significantly improved, where all of which are clinically relevant.

Now clearly, this is a drug that's approved for myeloma and potentially can be used in the clinical setting, particularly in those patients who also meet the criteria for myeloma where it would not necessarily be an off-label use. Clearly, what needs to be kept in mind when treating patients with light-chain amyloidosis is that they need to be watched very closely for any kind of toxicity, whether it be ixazomib-dexamethasone or another kind of treatment. Ongoing trials are looking at other novel agents, particularly daratumumab in combination with bortezomib, cyclophosphamide, and dexamethasone in a randomized trial, and other novel agents that are currently being studied in myeloma are also being studied in amyloidosis. So, hopefully we will see at least some of these agents being approved in this space in the next few years, which then will lead to improved outcomes for patients with light-chain amyloidosis.

Thank you for your attention.