Managing Myeloma

Results of the Pivotal STORM Study (Part 2) in Penta-Refractory Multiple Myeloma (MM): Deep and Durable Responses with Oral Selinexor Plus Low Dose Dexamethasone in Patients with Penta Exposed and Triple Class-Refractory MM

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I am live here at the American Society of Hematology meeting talking about a Phase II trial of selinexor treatment of refractory myeloma or the STORM trial. This trial is being presented here at the meeting this year by my colleague, Dr. Chari.

Multiple myeloma has seen tremendous advances over the past few years with the introduction of many effective agents; however, none of them are curative and most patients will eventually develop disease that is refractory to all of the available agents. When myeloma is refractory to all of the available agents, survival is overall very poor. Selinexor is a completely new class of therapeutic agent. It is a selective inhibitor of nuclear export, which means that it inhibits a protein XPO1, or exportin-1, that is responsible for shuttling other proteins out of the nucleus of the cell and into the cytoplasm. One of the central insights behind the development of selinexor is that one particular protein, XPO1, is responsible for shuttling most tumor suppressor proteins, the glucocorticoid receptor, and some mRNAs of oncoproteins which most cancer cells would like to keep out of the nucleus and in the cytoplasma of the cell by inhibiting XPO1-mediated transport of these tumor-suppressor proteins and the glucocorticoid receptor. Selinexor can decrease proliferation and survival of cancer cells in general and specifically augment the effectiveness of the dexamethasone and other corticosteroids which is of particular utility in treating multiple myeloma.

The STORM trial took patients with very refractory myeloma who had all received, essentially, every agent that we know is truly effective in myeloma. Patients had to be individually refractory to bortezomib. Patients had received each of the following medications: bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab, an alkylating agent and a glucocorticoid, and had to have disease that was documented to be refractory to at least one proteasome inhibitor, at least one immunomodulatory drug, daratumumab, a glucocorticoid, and their most recent therapy. These were heavily pretreated patients whose disease had become refractory to every class of medication that is truly effective for myeloma. Patients received oral selinexor given at a dose of 80 mg twice a week and dexamethasone given at a dose of 20 mg twice a week, so this was in all oral regimen. The patients were obviously very heavily pretreated; 96% of the patients were specifically refractory to carfilzomib, to pomalidomide, and to daratumumab, and 68% of patients were refractory to carfilzomib, bortezomib, lenalidomide, pomalidomide, and daratumumab. In this very heavily refractory patient population, the overall response rate to selinexor and dexamethasone was 26.2%, an additional 16 patients had a minimal response yielding a combined benefit rate of 39.3%. The median time to response was one month, and the median duration of response was 4.4 months.

The efficacy of selinexor was similar regardless of how refractory patients were to prior therapy, whether they had received daratumumab in their most previous line of therapy, and whether they had previously received daratumumab in combination with other agents. Median progression-free survival in this very refractory population was 3.7 months and median overall survival was 8.6 months, which actually compares favorably with historical controls with similarly refractory disease. Selinexor was associated with some significant side effects, primarily gastrointestinal side effects, nausea, anorexia, vomiting, and diarrhea. Constitutional side effects including fatigue, weight loss, and hyponatremia. These side effects were generally manageable with supportive care measures but many patients required dose reductions and dose interruptions. In addition, selinexor was associated with a significant amount of thrombocytopenia, with 23% having grade 3 thrombocytopenia and 31% having grade 4 thrombocytopenia. We also saw a significant amount of anemia and some neutropenia.

In conclusion, in this study of patients who were very heavily pretreated and essentially had no reasonable treatment options, selinexor, which is an oral, novel agent with a completely new mechanism of action, had an impressive overall response rate of 26.2%, and the responses lasted a median of 4.4 months in patients who otherwise would have had no good treatment options. We are hoping that selinexor will therefore prove to be a new treatment option for patients with very refractory myeloma, and ongoing trials are investigating the effect of adding selinexor to other treatment regimens including the Phase III Boston study comparing selinexor, bortezomib, and dexamethasone to the combination of bortezomib and dexamethasone alone.

Reference

Chari A, Vogl D, Dimopoulos M, et al. Results of the Pivotal STORM Study (Part 2) in Penta-Refractory Multiple Myeloma (MM): Deep and Durable Responses with Oral Selinexor Plus Low Dose Dexamethasone in Patients with Penta Exposed and Triple Class-Refractory MM. ASH 2018. Abstract 598.