IMWG STUDIES PATIENTS WHO HAVE EXHAUSTED THEIR TREATMENT OPTIONS

Myeloma Today in conversation with Dr. Shaji Kumar

Dr. Kumar, we would like to hear about your current research project on behalf of the International Myeloma Working Group (IMWG), but first please tell us about the 1999 Mayo Clinic study of myeloma patients whose disease relapsed?

Up until approximately 10 years ago, there were relatively few therapies available for treating multiple myeloma, and most of those therapies had been developed during the preceding 30 years. In 2000, investigators at the Mayo Clinic analyzed data pertaining to myeloma patients who were treated at the Clinic and whose disease came back after initial therapy. Here at Mayo, we have long-term follow-up on our patients, so we looked at patient outcomes from each time their disease relapsed from previous treatment. After each relapse, we measured how long the patient responded to subsequent treatment, and how long they lived after the treatment failed.

Shaji Kumar, MD
Associate Professor of Medicine
Division of Hematology
Mayo Clinic
Rochester, MN

What was the significance of that study?

That was a very interesting study because until that time we had not examined in detail what happened to myeloma patients post-relapse. Most of the investigations performed prior to that study focused on what happed after initial treatment up until the first relapse.

Please tell us about the study follow-up.

To follow up, we initiated a new study at Mayo Clinic in 2007, and our findings were published in *Blood* in early 2008. We looked at data from nearly 3,000 patients treated at the Clinic over a 36-year period. We separated the patients into six groups, based on the year of diagnosis. In the first four groups, which included patients diagnosed prior to 1994, we saw very little improvement in patient survival. We saw improvement in the survival of patients who were diagnosed between 1994 and 2000, with the data on the survival of patients diagnosed since 2000 being even better than for those who were diagnosed between 1994 and 2000.

How did you interpret those findings?

We think that what changed related primarily to two things: wider use and availability of stem cell transplantation, and the introduction of three novel anti-myeloma agents (thalidomide, lenalidomide, and bortezomib) that are very effective at treating the disease. We know that both these components played a role in our findings, because we saw improved survival in newly diagnosed patients and also in a smaller subset of patients who relapsed following a stem cell transplant. Of the three novel agents, lenalidomide and bortezomib have been proven to improve overall survival, both when used as part of initial anti-myeloma therapy and in the relapse setting.

Now please tell us about the analysis you are currently performing on behalf of the IMWG.

The IMWG project was undertaken to find out what happens to myeloma patients who have exhausted all their treatment options.

Over the last 10 years, we have seen a major shift both in available treatments and in the outcomes for patients with myeloma. In 2009, we are looking at a very different landscape of available anti-myeloma therapies. Over the past decade, survival of newly diagnosed patients has more than doubled. Data show survival improvement for each year following 2000, which is directly related to the role played in myeloma treatment by the three novel agents I mentioned earlier.

But we know that none of the three novel agents are curative, because the myeloma invariably comes back sooner or later. And the introduction of the novel agents has also brought forth new challenges. Because we have significantly improved the outcome for patients, the problem that we face today is that newer medications that need to be studied for myeloma have a much higher hurdle to overcome to demonstrate to the regulatory authorities that a new drug warrants investigation because it is likely to make a difference for patients. This means that it has become more difficult to show that newer drugs are able to improve survival ever more than the currently available medications. Clinical studies now require larger groups of patients, who must be followed for longer periods of time.

Doesn't that delay the process of getting the next promising anti-myeloma drug to patients?

That is exactly our concern. The three novel drugs currently available took four to five years to get to the marketplace. If the newer drugs follow the same path, it might take even longer to get them approved! Clearly, that is just too long to wait.

How does that relate to the current IMWG study?

We hope that by analyzing the outcome of patients who have failed on all available therapies the current IMWG study will accelerate the process of drug approval. If we can show that the newer drugs being studied offer a clear survival benefit to patients who have no remaining approved treatment options, this can become the new benchmark for evaluating newer compounds in clinical trials. This would help expedite bringing new useful compounds to market.

For this research project, we are collecting data on a group of patients who have become nonresponsive or refractory to all the novel agents available to them. The data is being provided by investigators at 13 myeloma centers (six in the US plus seven in Europe). The availability of novel agents varies from country to country, but the data gives us a broad global spectrum of the impact of the newer medications. We are looking at how these patients have been doing from the time they became unresponsive to available treatments.

Based on prior studies, we are targeting a group of 300 patients who have active myeloma and no remaining means to control the disease. We feel that this would give us enough data for a strong study leading to a good conclusion. The patients are not "enrolled" in this study in the traditional sense, as what we are doing is analyzing existing medical records of nonresponsive patients retrospectively, and tracking what happened to those patients over time.

Continues on Page 16