

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

Section Editor: Mark J. Ratain, MD

New Drugs for Multiple Myeloma

Kenneth C. Anderson, MD
Harvard Medical School
Dana-Farber Cancer Institute

H&O What significant advances in the treatment of multiple myeloma were reported at this year's Annual Meeting of the American Society of Clinical Oncology?

KA This year, there were quite a few exciting reports regarding the treatment of multiple myeloma, primarily centered on the use of thalidomide (Thalomid, Celgene) and the novel immunomodulatory drug lenalidomide (Revlimid, Celgene), which was just approved for the treatment of multiple myeloma by the US Food and Drug Administration (FDA). One of the most significant studies pertains to elderly patients with multiple myeloma. Dr. Thierry Facon and colleagues reported the results of a study demonstrating markedly enhanced antimyeloma activity when thalidomide was added to oral melphalan plus prednisone, a combination that has been the standard treatment for elderly patients for over 50 years.

H&O Could you briefly describe the history of the use of thalidomide in the treatment of multiple myeloma?

KA Initial studies of thalidomide in the treatment of multiple myeloma found this agent to be associated with a 50% decrease in myeloma protein in approximately 30% of patients with relapsed/refractory disease. Subsequently, thalidomide in combination with dexamethasone was shown to achieve responses in about half of patients with relapsed/refractory disease who did not respond to either agent given alone.

Thalidomide plus dexamethasone has since been used in the first-line treatment of multiple myeloma, achieving responses in approximately two thirds of patients and enabling the collection of stem cells. This combination is now the most common approach used to prepare patients for stem cell transplantation.

H&O Were the patients enrolled in the study by Facon and colleagues candidates for transplantation?

KA No, the patients in this study were elderly non-transplant candidate patients, which is very significant. The investigators compared melphalan/prednisone with melphalan/prednisone/thalidomide and with melphalan (100 mg/m²) given twice with stem cell rescue after each administration—in other words, a transplantation-oriented approach. Remarkably, there was a greater than 90% reduction in myeloma protein among 50% of the patients receiving melphalan/prednisone/thalidomide. The event-free survival of 28 months associated with the triple combination arm was longer than that seen in the other arms, as was the overall survival of 54 months. The toxicity profile was very manageable. This study is one of the first to compare a novel antiangiogenic therapy combined with conventional treatment with a transplantation approach in which the former proved superior.

In addition, the findings of this study confirm an earlier Italian study reported by Palumbo and associates in *Lancet*, showing the superiority of melphalan/prednisone/thalidomide compared with melphalan/prednisone. The clear benefit that thalidomide confers in terms of response rate and event-free and overall survival is a very exciting advancement for the treatment of multiple myeloma. There are other promising novel agents being investigated for this disease, but the studies by Facon and colleagues and Palumbo and associates, in which a novel agent combined with conventional therapy achieves unprecedented levels of response and benefit, is changing the paradigm for future clinical trials. Both bortezomib (Velcade, Millennium Pharmaceuticals) and lenalidomide have been preliminarily studied in combination with melphalan/prednisone for the treatment of elderly patients with multiple myeloma and both have been found to increase the response rate, the extent of the response, and event-free survival.

H&O How does lenalidomide differ from thalidomide?

KA Lenalidomide is a more potent inhibitor of cytokines and a more potent stimulator of T-cell proliferation than

thalidomide. Earlier phase I studies found lenalidomide to elicit a remarkable response rate, even in advanced disease, with a noteworthy lack of somnolence, constipation, and neuropathy, all of which are associated with thalidomide.

H&O Could you describe recently reported studies of lenalidomide?

KA At the 2005 meeting of the American Society of Hematology, Dr. Meletios Dimopoulos and associates reported during the Plenary Session the results of a primarily European study evaluating dexamethasone with or without lenalidomide in the treatment of relapsed multiple myeloma. The data showed a higher overall response rate, a longer duration of response, and a prolongation of time to progression associated with the combination arm, all of which were statistically significant.

Six months later, at this year's annual meeting of the American Society of Clinical Oncology (ASCO), Dr. Donna Weber and colleagues reported the results of a North American study of lenalidomide in combination with dexamethasone compared with dexamethasone alone in the treatment of relapsed multiple myeloma. The results were very similar to those reported by Dimopoulos and associates. In the study by Weber and colleagues, overall survival time was also statistically significantly improved among patients receiving the combination.

These two studies provided the framework for the recent FDA approval of lenalidomide.

H&O How would you summarize these recent findings?

KA In summary, thalidomide, lenalidomide, and bortezomib are three significant new drugs in the armamentarium for the treatment of multiple myeloma. Each of these was used first as a single agent for the treatment of advanced disease and then combined with conventional agents such as dexamethasone for transplant candidates, or melphalan/dexamethasone for non-transplantation candidates. In all settings, these combinations have achieved improvements in overall response and survival. The paradigm that these approaches represent is that of targeting the tumor cell and its microenvironment in order to overcome resistance to traditional chemotherapy and thereby markedly improve outcome.

H&O How is the success of new therapies for the treatment of multiple myeloma affecting the development of new drugs?

KA The success of recent new approaches indicates that novel therapies targeting the tumor, the tumor-host interaction, and the bone marrow microenvironment can overcome conventional drug resistance. Novel agents have

shown very impressive activity alone and in combination with conventional drugs in patients with advanced disease, and even more impressive activity when used as the initial treatment for newly diagnosed patients.

Now that these agents have been developed and others are on the horizon, we will be able to combine drugs in order to enhance cytotoxicity, overcome drug resistance, and create a more favorable side effect profile. It is hoped that once additional combinations that achieve high overall and complete response rates have been clearly identified, clinical trials can be conducted in which administration of the highly active combination is followed by stem cell harvesting and then randomization to high-dose therapy plus transplantation early or later, at the time of relapse. This approach will enable measurement of the durability of the response to this combination, which needs to be determined, particularly in newly diagnosed patients.

The advances made in the treatment of multiple myeloma now represent a model for rapid bench-to-bedside translation of new drugs. The teamwork approach among academia, the pharmaceutical industry, the FDA, the National Cancer Institute, and patient advocacy groups, all working toward the common goal of expediting progress, certainly serves as a useful example. As a result of this cooperation, the normal time needed for bench-to-bedside development of 7–10 years has been shortened to 3–5 years.

Also, these recent advances illustrate the potential importance of expanding the spectrum of potential drug targets to include not only the tumor cell but also the tumor-host interaction and the tumor microenvironment. This shift results in a marked increase in the number and range of targets. Agents directed at these targets can be designed to overcome resistance mechanisms that are both intrinsic to cancer cells and also extrinsic to cells and related to various factors in the tumor microenvironment.

H&O What other classes of agents are showing promise in the treatment of multiple myeloma?

KA Inhibition of Hsp90 is a very interesting approach. Preclinical data suggest that Hsp90 is constitutively elevated in multiple myeloma cells and serves as a chaperone protein implicated in growth, survival, and drug resistance signaling pathways. Preclinical data also suggest that Hsp90 is required for the unfolding of ubiquitinated protein and its degradation in the proteasome. Based on these observations, it was hypothesized that Hsp90 would be an effective therapeutic target for this disease. A single-agent trial of the Hsp90 inhibitor KOS-953 (Kosan Biosciences) has already shown some promising activity.

Laboratory studies found that treating multiple myeloma cells with bortezomib further induces Hsp90. Following bortezomib, treatment with KOS-953 to

inhibit that response resulted in synergistic cytotoxicity in the preclinical setting.

At this year's ASCO meeting, results of a phase I clinical trial of KOS-953 plus bortezomib were reported. The findings showed that the addition of KOS-953 to bortezomib sensitizes multiple myeloma cells to proteasome inhibition, thereby overcoming resistance to bortezomib.

Suggested Reading

Facon T, Harousseau MJ, Huguier F, et al; on behalf of the Intergroupe Franco-phonie du Myélome. Superiority of melphalan-prednisone (MP) + thalidomide (THAL) over MP and autologous stem cell transplantation in the treatment of newly diagnosed elderly patients with multiple myeloma. *Proc Am Soc Clin Oncol*. 2006;24(18S pt 1). Abstract 1.

Weber DM, Chen C, Niesvizky R, et al. Lenalidomide plus high-dose dexamethasone provides improved overall survival compared to high-dose dexa-

methasone alone for relapsed or refractory multiple myeloma (MM): results of a North American phase III study (MM-009). *Proc Am Soc Clin Oncol*. 2006;24(18S pt 1). Abstract 7521.

Chanan-Khan A, Richardson P, Alsina M, et al. Phase 1 clinical trial of KOS-953 + bortezomib (BZ) in relapsed refractory multiple myeloma (MM). *Proc Am Soc Clin Oncol*. 2006;24(18S pt 1). Abstract 3066.

Palumbo A, Bringhen S, Caravita T, et al; Italian Multiple Myeloma Network, GIMEMA. Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: randomized controlled trial. *Lancet*. 2006;367:825-831.

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H&O What studies are needed in order to answer these questions?

JM Advancements in the understanding of TRALI will depend on well-designed clinical trials. However, there are currently no ongoing trials on the scale that would be necessary to conclusively study even the incidence of TRALI. More questions may need to be answered before such a trial could be conducted. First, clinicians need to agree on a common definition of TRALI: What is the meaning of acute lung injury? How low does the oxygen saturation need to fall in order to qualify as TRALI? What should appear on a chest radiograph? How soon does the reaction need to occur relative to the transfusion? Progress has been made over the past several years in developing a consensus definition of TRALI through publications at

various conferences. The next step is to carefully design meaningful clinical trials so that we can clearly determine the incidence of TRALI and identify patient and serologic factors that may be important.

Suggested Reading

Mair CD, Hirschler N, Eastlund T. Blood donor and component management strategies to prevent transfusion-related acute lung injury (TRALI). *Crit Care Med*. 2006;34(5 suppl):S137-S143.

Silliman CC. The two-event model of transfusion-related acute lung injury. *Crit Care Med*. 2005;34(suppl 5):S124-S131.

Curtis BR, McFarland JG. Mechanisms of transfusion-related acute lung injury (TRALI): anti-leukocyte antibodies. *Crit Care Med*. 2006;34(5 suppl):S118-S123.

Silliman CC, McLaughlin NJ. Transfusion-related acute lung injury. *Blood Rev*. 2006;20:139-159.

Toy P, Popovsky MA, Abraham E, et al. National Heart, Lung and Blood Institute Working Group on TRALI. Transfusion-related acute lung injury: definition and review. *Crit Care Med*. 2005;33:721-726.