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Myeloma Therapy—A New Paradigm

Archie W. Brown, Jr., MD

Section of Hematology and Oncology, Ochsner Clinic Foundation, New Orleans, LA

Multiple myeloma causes about 11 000 deaths each year in the United States. For decades, treatment has been based on alkylating agent chemotherapy and corticosteroids. Results have improved with the use of high-dose alkylator chemotherapy and peripheral stem cell rescue, the toxicity of which is usually tolerated in patients who are healthy other than having myeloma. New drugs with novel mechanisms of action are being developed; these are not curative, but there is already evidence of high response rates; improved survival; and, for some patients, alteration of the nature of this disease into an episodic illness requiring intermittent treatment.

In the 1950s thalidomide was marketed in Europe as a hypnotic and an antiemetic. As a consequence of its teratogenic effects, thousands of children were born with physical deformities, primarily phocomelia. Although never approved by the Food and Drug Administration (FDA), thalidomide was taken by many Americans because at the time ''experimental'' drugs could be distributed before FDA review. As a consequence of the ''thalidomide babies,'' the FDA was given far more authority to mandate the safety of pharmaceuticals.[1]

Thalidomide did not disappear. It was soon found to suppress the painful inflammatory dermal complications of leprosy. Antiangiogenic properties were confirmed, and potent inhibition of tumor necrosis factor-alpha was detected. Thalidomide and its analogs (lenalidomide and thalidomide have both been approved for the treatment of myeloma) also induce other inflammatory cytokines, expand natural killer cells, modulate cell adhesion molecules, and induce apotosis of myeloma cells. The therapeutic benefits of these drugs are largely mediated by their effects on the bone marrow microenvironment as opposed to direct effects on myeloma cells.

These are not cytotoxic agents, and their side effects are generally not those of traditional chemotherapy drugs. Lenalidomide and thalidomide both carry an increased risk of venous thrombosis. Thalidomide more commonly causes sedation, peripheral neuropathy, constipation, and fatigue, whereas myelosuppression is more common with lenalidomide.

The section of Hematology and Oncology at Ochsner participated in the pivotal clinical trial[2] leading to FDA approval of lenalidomide with dexamethasone therapy in relapsed myeloma patients. This study and a similar investigation[3] in Europe showed that, compared with dexamethasone alone, the addition of lenalidomide tripled the response rate (to 60%), more than doubled the duration of response (to 11 months), and improved survival (30 months versus 20 months).

With the use of lenalidomide and dexamethasone as initial therapy for myeloma, early reports[4] have described response rates above 90%. Likewise, bortezomib, a drug whose primary mechanism of action appears to be proteosome inhibition, was recently approved by the FDA. It also has remarkable antimyeloma activity when combined with melphalan and prednisone[5] or thalidomide and dexamethasone.[6]

These pharmaceuticals are the first agents in more than four decades that are altering the natural history of multiple myeloma. With other clinical trials, we are beginning to learn when these drugs should be employed; in what combination; and whether, for some patients, they can supplant stem cell transplantation.

Address correspondence to:
Archie W. Brown Jr., MD
Section of Hematology and Oncology
Ochsner Clinic Foundation
1514 Jefferson Highway
New Orleans, LA 70121

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