FEATURE ARTICLE

Understanding Novel Therapeutic Agents for Multiple Myeloma

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Multiple myeloma, a B cell malignancy of the plasma cells, remains incurable. Advances in high-dose chemotherapy and stem cell transplantation have improved overall survival and event-free disease periods, but relapses are inevitable. New therapeutic agents have shown promising clinical use in patients with relapsed or refractory multiple myeloma. This article discusses the therapeutic applications of these novel agents with a focus on immunomodulatory drugs, proteasome inhibitors, and arsenic compounds.

Key Words: multiple myeloma, stem cell transplantation, antineoplastic protocols

Multiple myeloma (MM) is a B cell malignancy of the plasma cells. It is the second most common hematologic malignancy; only non-Hodgkin's lymphoma is more common. About 14,600 cases of MM will be diagnosed in 2003, and approximately 10,900 people will die of the disease (Jemal et al., 2003). Recently published data on cancer incidence and mortality indicate a consistent decline in mortality rates for most cancers from 1991–1995. However, MM is one of three cancers that showed increased mortality rates for men and women, with increases of 5.6% and 3.6%, respectively (McKean-Cowdin, Feigelson, Ross, Pike, & Henderson, 2000).

People affected by MM often are elderly, with a median age at diagnosis of 65 years. Eighty percent of patients are older than 60 years, and less than 3% are younger than 40 years. African Americans are affected by the disease twice as often as Caucasian Americans. MM is one of the leading causes of cancer death among African Americans (Blade, Kyle, & Greipp, 1996).

MM results from clonal proliferation of plasma cells, which produce a homogeneous immunoglobulin fraction detectable in the serum or urine, called myeloma protein or M-spike. Bone destruction caused by the production of osteoclastic factors by malignant plasma cells is the most characteristic feature of MM, and bone pain is the predominant presenting symptom. Other presenting symptoms include anemia, uremia, recurrent infections, and, less commonly, hypercalcemia, hyperviscosity, polyneuropathy, and spinal cord compression (Lokhorst, 2002).

An oral regimen of melphalan and prednisone was the most frequently used treatment for newly diagnosed MM from 1970–2000. The mean survival rate with this regimen is about 72 months (Trippoli, Messori, Becagli, Alterini, & Tendi, 1998). Clinical trials have tested numerous regimens to improve mean survival from time of diagnosis, but, until recently, none was found to be superior to melphalan and prednisone (Hjorth et al., 1999; Myeloma Trialists' Collaborative Group, 1998).

Recent articles have reviewed the main therapeutic regimens for managing patients with MM (Campbell, 2002; Rajkumar, Gertz, Kyle, & Greipp, 2002; Weber, 2002). The efficacy and safety of high-dose chemotherapy (HDC) and autologous stem cell transplantation is well established in myeloma and considered standard therapy (Goldschmidt et al., 1997; Singhal, 2002). HDC has been used for more than 10 years as treatment for MM, either alone or with autologous hematopoietic stem cell rescue. It has improved remission, event-free survival, and overall survival rates in patients with MM (Attal & Harousseau, 1997; Harousseau & Attal, 1997).

At least one-third of patients with MM do not respond to induction chemotherapy, and those who initially achieve remission (even with HDC) eventually relapse and require additional treatment (Kyle, 1999). Because MM remains incurable and relapse is inevitable, a great need exists for novel therapeutic agents that can prolong life and improve overall survival rates for patients with MM.

Immunomodulatory Drugs

Thalidomide (Thalomid®, Celgene Corporation, Warren, NJ), used empirically to treat MM based on its antiangiogenic activity and the increased angiogenesis observed in MM bone marrow, achieves responses even in refractory, relapsed disease (Singhal et al., 1999). However, thalidomide has significant and dose-limiting side effects (Tariman, 2003), including somnolence, constipation, and neuropathy, which have prompted the search for more potent and less toxic thalidomide derivatives (Richardson, Schlossman, et al., 2002).

Preclinical Studies

Immunomodulatory Drugs (IMiDs™) are potent thalidomide derivatives or analogs that markedly stimulate T cell proliferation, as well

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