Overview of the Advances in the Treatment of Multiple Myeloma

In this issue of *Cancer Control*, we are privileged to include four excellent manuscripts addressing recent advances made in the understanding of the biology and treatment of multiple myeloma. Multiple myeloma is a neoplastic disease of B-cell lineage resulting in the overproliferation of malignant plasma cells. The actual origin of the malignant cell is unknown but may originate from pre-B cells. The annual incidence of myeloma in the United States is approximately 4 to 5 per 100,000, with 14,000 estimated new cases diagnosed each year. American blacks have nearly double the incidence compared to whites.

The clinical spectrum of myeloma includes bone damage, increased infections, and anemia. The median survival of patients with myeloma depends on the stage of disease at diagnosis, but it is approximately 3.5 years for all patients. Only approximately 5% of patients will be alive at 10 years following diagnosis. Despite the use of many different chemotherapeutic regimens, there has been little improvement in outcome since the introduction of melphalan and prednisone over three decades ago. Chemotherapy induces remissions in approximately 50% of cases with median remission times of two years. In this issue, Drs Lust, Donovan, Oken, Shustik, and Bensinger review some of the advances being made in the understanding of myeloma biology and how this information may be translated into improved therapy.

Understanding the pathogenesis and progression of myeloma will likely provide us with new approaches to treating the disease. In the report by Drs Lust and Donovan, the progression from MGUS (a clinically benign condition associated with monoclonal gammopathy) to overt symptomatic myeloma is discussed. MGUS is considerably more common than myeloma, and as many as 25% of patients with this disorder will develop myeloma or related plasma cell disorders. While the clinical evolution of MGUS to overt myeloma has been well described, cellular mechanisms have been only recently described that may be causally related to this progression. Studies have shown that the multistep pathogenesis from MGUS to myeloma may be related to cytokines such as IL-6 and IL-1β, adhesion molecules, viruses, and certain oncogenes. If a causal relationship is determined to exist for these factors, then new targets for therapy of myeloma may emerge.

For over three decades, the standard treatment for myeloma has been the combination of melphalan and prednisone (MP). Attempts to improve on results of MP by using multiagent regimens have been disappointing overall. Clearly, some regimens may be superior to others in certain situations, such as preference for the use of vincristine, doxorubicin, and dexamethasone (VAD) in patients with acute renal insufficiency; however, little improvement in overall survival is seen with combination chemotherapy compared to MP. Difficulties in discerning whether combination chemotherapy is superior to MP are discussed in the article by Dr Oken. He also points out that advances in supportive care have been made recently, and these include the use of erythropoietin for anemia, G-CSF for treatment-related myelosuppression, and pamidronate for the prevention of bone destruction. Ultimately, however, newer agents with novel mechanisms of action will need to be developed to improve treatment outcome for the majority of myeloma patients.

One approach to improving survival is to try to prolong treatment response using biological modifiers such as interferon. Dr Shustik reviews the results of multiple studies using interferon in the treatment of myeloma. He concludes that interferon has, at best, a modest effect on overall survival when combined with induction chemotherapy or when used as maintenance therapy. However, he also suggests that recognizing certain subsets of patients who might benefit from interferon may be important and that cost-benefit analyses combined with quality-of-life data must be considered when developing guidelines for the use of interferon in the treatment of myeloma.

Perhaps the greatest advance in the treatment of myeloma has been the use of very high-dose chemotherapy and autologous or allogeneic hematopoietic stem-cell transplantation (HSCT). Dr Bensinger reviews the results of numerous trials including prospective, randomized studies that demonstrate that autologous HSCT results in superior response rates, progression-free survival, and disease-free survival when compared to conventional-dose chemotherapy. Allogeneic HSCT may even result in long-term survivals (cures?) but at significant cost, including high risk of early death due to complications. Dr Bensinger highlights the challenges that must be met in order to improve results and make the HSCT option available to more patients.

These four excellent reviews illustrate the current approach to the treatment of myeloma. They also identify some of the most challenging issues that must be met in order to improve treatment outcome. Our efforts must now focus on improving our understanding of the biology of myeloma so that newer, more novel approaches may be developed to treat this as yet incurable disease. *Carpe diem!*

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