

## Multiple Myeloma: Increasing Our Treatment Options

Multiple myeloma is a malignancy characterized by the proliferation of clonal plasma cells preferentially in the bone marrow. The second most common hematologic malignancy, this diagnosis is newly made in 35,000 persons yearly worldwide.

Over 40 years ago, Bergsagel and others showed that a combination of melphalan and prednisone was an effective chemotherapy regimen in myeloma, inducing responses in over 50% of newly diagnosed patients. For decades, this simple combination remained the standard treatment for myeloma since other chemotherapy regimens failed to show improved survival when compared to it. It was not until 1995, when high-dose chemotherapy plus peripheral stem cell transplantation was determined to be superior to standard chemotherapy in a randomized trial, that we finally had evidence of a positive change in both disease-free survival and overall survival.

Even though little progress was made in the treatment of these patients before high-dose chemotherapy, significant progress was being made in understanding the biology of the disease. We have come to understand the molecular mechanisms of growth and apoptosis in myeloma, and we now appreciate the major contribution of the bone marrow microenvironment to the tumor growth, resistance to chemotherapy, and bone destruc-

tion. It is clear that successful management of myeloma requires targeting not only the malignant cell, but also the microenvironment. This has led to the development and evaluation of novel therapies that can exert this dual effect. Fortunately, several drugs have recently made the transition (translation) from the bench to the clinic and have had a significant impact on the treatment of myeloma patients.

In this issue, we are privileged to include contributions from myeloma investigators who have directly contributed to the development and evaluation of several novel targeted therapies. The rapid development of bortezomib reflects the depth of the new understanding of cancer disease pathways and the effect of proteasome inhibition on those pathways. Drs. Richardson and colleagues trace the development of this intervention from basic biology to its availability and effectiveness for treating patients. Dr. Hussein then describes the potential mechanisms of action of arsenic in patients with myeloma, and he summarizes the clinical data now available on its use. Thalidomide is no longer just seen as a cause of severe developmental defects. This drug, given alone and with dexamethasone, produces remissions in patients with myeloma. Dr. Weber reviews these data and describes the different toxicity and the anti-tumor outcomes from using the thalidomide analog IMiD-3 in the

disease. Finally, I review with Drs. Santucci, Mackley, and Sebti the recent work on farnesyltransferase inhibitors that are now being tested clinically in several different tumor types, including myeloma.

These are exciting times in myeloma research. The hard work of many investigators around the world is beginning to pay off. Not considered in this issue is the work on gene expression profiles that should allow the definition of a patient-specific genetic assessment that can allow us to more accurately target therapy. Through this issue, we wish to acknowledge the work of the many myeloma investigators around the world. We especially want to recognize the thousands of patients with myeloma who have participated in clinical trials, thereby providing an invaluable contribution to the recent progress in the treatment of this still lethal disease.

In addition to the articles focusing on the novel targeted therapy in the treatment of myeloma, Dr. Simon and colleagues describe the outcomes from use of a different targeted therapy in a different tumor type, lung cancer. This was not a randomized trial, but rather a "landmark" analysis of those patients who had taken gefitinib for at least 12 weeks, ie, they had reached the 12-week landmark. This report provides a sense of what effects on advanced lung cancer gefitinib might have when used in the community. Dr. Chrischilles

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and colleagues describe the detrimental effect on survival of early cessation of CHOP chemotherapy for non-Hodgkin's lymphoma. Early termination was usually associated with neutropenic fever in the first treatment cycle. Dr. Vincent and coworkers then discuss the use of voriconazole, a new triazole that was utilized to successfully treat disseminated cerebellar *Fusarium* infection. Finally, Dr. Jakub and colleagues describe an interesting case that induces us to think about and use the new 2003 AJCC TNM classification for breast cancer.

Yes, it is a full issue and we hope you will enjoy and benefit from reading it.

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