Plasma Cell Disorders: An Historical Perspective

Nikhil C. Munshi

Five decades ago myeloma was an enigmatic disease recognized as having plasma cell infiltration in the bone marrow (BM) and presence of recently identified clonal immunoglobulin heavy and light chains in serum along with bone lesions. No effective systemic therapy existed, and urethane, with anecdotal activity, was found to be inferior to placebo in a randomized study! Since then rapid progress in our understanding of the pathobiology of the disease has led to both improvement in diagnostic techniques as well as therapeutic options and outcome.

The advances in diagnostic methods in last 50 years have included immunofixation to identify low-level presence and type of clonal paraprotein in 1960s, to measurement of serum free light chain in the last 5 years to evaluate the disease activity, especially in patients with oligo secretory disease or renal failure, and to define stringent complete response (CR). Although skeletal survey remains a standard investigative procedure, since the 1990s MRI has been a sensitive method to evaluate both bone lesions and BM involvement. The traditional quantitation of myeloma cell in BM was supplemented with cytogenetics in the 1980s, FISH examination in the 1990s, and multicolor immunoflorescence analysis to identify malignant plasma cells in the 2000s. The ongoing studies investigate genomic and proteomic characteristics to develop improved prognostic models and eventually formulate individualized therapy.

There have been three distinct phases in development of therapy for multiple myeloma (MM). First, in the 1960s, melphalan was confirmed as the first active antmyeloma agent. The combination of melphalan with prednisone (MP) became one of the standards of therapy. Even with more complex chemotherapy regimens, CR was rare and all patients ultimately relapsed. The next improvement in therapy was high-dose chemotherapy supported by autologous stem cell transplant (ASCT) in the 1980s. In randomized studies, ASCT was found to be superior to conventional chemotherapy, and became the standard of care, achieving high CR and improved survival. CR achievement was shown to be associated with longer progression-free and overall survival leading to its introduction as a major endpoint in clinical trials.

The third and most recent advance has been our understanding that the BM microenvironment supports myeloma cell growth, survival and development of drug resistance. This has led to a change in the treatment paradigm to target not only the tumor cells but also the BM microenvironment. Four new drugs—thalidomide (T), bortezomib (V), lenalidomide (R), and pegylated-liposomal doxorubicin—have been approved for myeloma in last five years, completely changing the therapeutic scenario. Patients who are not candidate for transplant now receive MPT or MPV. In younger patients, these novel agents are now part of standard induction regimen improving results of ASCT. The three-drug combination of RV with dexamethasone achieves response in 100% patients and raises question about the need and place of transplant in myeloma.

Recent advances in high density, high through-put array technology have enabled the interrogation of genomic changes both at DNA and transcriptional levels, allowed for molecular classification of myeloma, and provided the scientific rationale for novel targeted therapies; in 2007, 13 new agents were undergoing clinical evaluation in myeloma. The median OS before therapy was 6 months; this improved to 3 years following MP treatment and is now greater than 7 years. In one study, 10-year continued CR rate following novel agent therapy and ASCT has been 12%, suggesting that we are on the threshold of curative outcome in this disease.