An update on the management of multiple myeloma and amyloidosis

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Multiple Myeloma: Multiple myeloma (MM) is the second most common hematological malignancy in this country affecting nearly 20,000 patients each year with nearly 12000 deaths during the same period.[1] The treatment of MM has undergone a paradigm change in the past decade resulting in improved outcome of these patients. In fact, recent studies suggest that the median survival has nearly doubled in the past decade as a result of the improvements in treatment as well as supportive care measures.[2, 3] The most significant changes in treatment approach have included more widespread use of high-dose therapy for younger patients considered eligible for this procedure and the introduction of three novel drugs namely thalidomide, it analogue lenalidomide and the proteasome inhibitor bortezomib. Multiple Phase 3 clinical trials have demonstrated the clinical utility of these treatment approaches both in the setting of newly diagnosed as well as relapsed MM.[4-7] The current approach to treatment of patients with MM has been built upon the results of multiple clinical trials that have been conducted during the past decade. Improvements in the treatment have been paralleled by improvements in diagnosis, prognostication, disease monitoring as well as better understanding of disease biology.

Establishing the diagnosis of MM requires demonstration of clonal plasma cells, usually accompanied by presence of monoclonal protein in the serum or urine.[8] Symptomatic MM requiring treatment, in addition has end organ damage that can take the form of hypercalcemia, renal dysfunction, bone lesions or anemia as most common features. Introduction of the serum free light chain assay has enabled us to detect presence of

monoclonal protein in the in the majority of the patients who were previously considered to have non-secretory or oligo-secretory disease.[9] A variety of different prognostic factors have been identified in MM during the past years. There is considerable genetic heterogeneity in MM, but the patients can be broadly classified into those having a IgH translocations or hypodiploid MM and those with hyperdiploid MM characterized by trisomy of odd numbered chromosomes.[10] In particular, patients with t(4;14), and t(14;16) have a poor prognosis. Abnormalities like deletion of p53 and deletion of chromosome 13 detected by metaphase cytogenetics also are markers of poor outcome. More recently, use of sophisticated genetic analysis methods such as gene expression profiling in at a CGH have allowed us to understand the genetic basis of the deceased better, however these methods are still not ready for routine clinical use. Combining the genetic and conventional prognostic factors like proliferation status of MM cells, the B2 microglobulin and LDH levels allows us to develop a risk classification system.[11]

The initial approach to treatment of patients with newly diagnosed MM depends to a large extent on the ability of the patient to undergo SCT.[11] In general, the initial treatment approaches should be able to rapidly reverse disease related complications, alleviate symptoms, and decrease the risk of early death with minimal toxicities. For patients considered transplant eligible, the initial therapy should not have any deleterious effect on the ability to collect stem cells. The majority of the clinical trials done during the past few years have focused on how best to use the novel agents in the initial therapy of MM patients. Multiple Phase 3 trials have been performed examining these novel agents in combination with dexamethasone or as part of multidrug combinations for the initial

therapy. Several important results have come out of the studies. With the new regimens, early mortality rate of MM has significantly decreased with one-year survival rates of over 95% when one or more of these agents are used up front. Second, use of lenalidomide or bortezomib or a combination of both along with dexamethasone has resulted in very high response rates including complete response rates previously unseen outside the context of SCT. As a result patients are going into SCT with deeper responses than they had previously been able to. This in turn has improved the progression free survival of these patients following SCT even though the impact on the overall survival is still to be demonstrated. Other clinical trials are currently looking at incorporation of bortezomib into the conditioning regimen to further enhance the efficacy of SCT. Prior to the introduction of the new drugs, the median duration of response following an early SCT had been 18 to 24 months. Recent trials have shown that maintenance therapy with thalidomide can improve both progression free and overall survival in these patients. Ongoing trials are looking at the role of lenalidomide as maintenance therapy. The high response rates seen with the novel agents have also raised questions about the role of SCT in the current era. Based on the current data one can conclude that the introduction of novel agents by virtue of the high response rates allows us to safely considered delaying SCT until the first relapse. Whether SCT can be completely abandoned can only be decided on the basis of prospective clinical trials. In patients considered not eligible for SCT initial treatment approaches have included thalidomide or bortezomib in combination with melphalan and prednisone. Phase 3 clinical trials have shown improved overall survival when thalidomide or bortezomib is combined with melphalan and prednisone. It remains unclear if initial therapy with one of the new drugs versus another has any long-term implications. However, retrospective

analysis of existing clinical trials have suggested that the use of bortezomib maybe associated with the ability to overcome the adverse effect of poor risk genetic markers such as deletion 13 and t(4,14). In addition, use of bortezomib is encouraged in patients with renal insufficiency at time of presentation given its non-renal elimination. The advantage if any, of using multidrug combination regimens incorporating several novel agents compared to their sequential use has not been proven. However, ongoing clinical trials are addressing these questions. The treatment options for patients with relapsed MM have also significantly improved. Among the new drugs that are undergoing clinical trials, the most promising ones include the thalidomide analog Pomalidomide, the new proteasome inhibitor Carfilzomib and the HDAC inhibitor SAHA. In fact, pomalidomide and carfilzomib have been shown to be active in patients who are refractory to lenalidomide or bortezomib respectively. The increasing rate of response in with the new therapies has mandated a revision in the response criteria. The International Myeloma Working Group recently published consensus response criteria that incorporate a stringent CR category in addition to the CR, requiring normalization of free light chains and absence of clonal plasma cells in the bone marrow by immunophenotyping. Additional flow cytometry-based methods for detecting minimal residual disease are currently being evaluated and will likely form part of future response criteria.

Light Chain Amyloidosis (AL): AL is characterized by multiorgan deposition of light chain derived amyloid fibrils. In contrast with MM, AL is associated with relatively lower tumor burden.[12] The outcome of patients with AL, especially when there is severe cardiac involvement is poor. Treatment approaches for AL have undergone significant change over the past decade, partly driven by a better understanding of the disease behavior as well as

the parallel improvements in therapy of MM.[13] There have been increasing use of SCT with case control studies demonstrating that such an approach can improve the outcome. However, increasing experience with this modality has enabled us to better select patients for SCT. This has led to decreased transplant related mortality during the last few years. Currently SCT is offered to patients with limited number of organs involved and no significant cardiac involvement as determined by use of cardiac biomarkers.[14] Introduction of the melphalan and dexamethasone combination (MD) has opened up options for patients who are ineligible to undergo SCT.[15] Studies with this combination have demonstrated a hematologic and organ response rates comparable to SCT. This regimen appears to be well tolerated and may allow some patients who are initially ineligible for a SCT to proceed to SCT subsequently or collect stem cells for future SCT. Given its success in MM, thalidomide and lenalidomide have been studied in AL. While there clearly is activity as shown by hematological responses, the use of thalidomide has been associated with significant toxicity.[16] Lenalidomide is also an active drug in AL. However the toxicity still remains high, especially among patients with cardiac involvement in necessitating use of lower doses of drugs.[17] Both drugs have been studied in combination with cyclophosphamide with the reasonable toxicity and good efficacy. More recent trials have evaluated the role of bortezomib for treatment of AL. It has been associated with the relatively rapid light chain response with high rates of organ response. Currently a phase 3 clinical trial is ongoing that is comparing the MD to bortezomib plus MD. Ongoing trials are also comparing the role of SCT with the non-transplant therapies that are currently available. In summary, we have made significant advances in understanding the prognostic factors in patients with AL and this in turn has helped us tailor the therapy for these patients.

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