ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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Risk of Early Death in Multiple Myeloma

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H&O What are the survival outcomes following diagnosis of multiple myeloma?

SK Survival has clearly improved over the past decade. As of 10 years ago, the median survival of patients was 3–4 years. Today, it is approximately 8 years and improving. What is also clear is that survival is improving not only during the early part of the disease, but continuously throughout the disease course. In our experience at the Mayo Clinic, patients treated in the past 5 years seem to be doing better than the patients who were seen in the 5 years prior to that. However, approximately 25% of myeloma patients still die within the first 3 years of their disease, and approximately 10% of patients die within the first year. So, one area that still needs significant improvement is the number of patients who are dying within the first year following diagnosis.

H&O What are the treatment options in multiple myeloma, and which patients require specialized care?

SK There are many new drugs available, such as proteasome inhibitors and immunomodulatory drugs, which have decreased the proportion of patients who are dying within the first year of diagnosis. Numerous phase III trials, such as the Eastern Cooperative Oncology Group (ECOG) E1A00 trial, have examined these novel agents in combination with dexamethasone or as part of multidrug combinations for initial therapy. Some notable results have emerged from these studies. With the new regimens, early mortality rates have significantly decreased when 1 or more of these agents are used upfront. In addition, the use of lenalidomide (Revlimid, Celgene) or bortezomib (Velcade, Millennium Pharmaceuticals), 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 transplant.

Increasingly, it has been recognized that dose reductions of many myeloma therapies may benefit elderly patients, in whom the delivery of standard-dose therapy is difficult. In the MM-009 and MM-010 trials, treatment-related toxicities that prompted dose reductions of lenalidomide (from a starting dose of 25 mg) were more common in elderly patients and in patients with renal impairment. Lower doses of lenalidomide are better tolerated in this patient group. Similarly, the use of lower-dose bortezomib (weekly as opposed to twice weekly) appears to produce fewer neurologic and nonhematologic toxicities without compromising efficacy. Dose reduction of corticosteroids is often warranted in elderly patients as well, in whom diabetes, mood disorders, and increased risk of infections are more common.

H&O How does a risk-adapted therapy strategy affect the treatment approach?

SK At the Mayo Clinic, newly diagnosed myeloma is stratified into standard-, intermediate-, and high-risk disease using the strategy known as mSMART (Mayo Stratification for Myeloma and Risk-adapted Therapy). It allows a risk-based approach to therapy, maximizing benefit, and, at the same time, helps to minimize the impact on the patient's quality of life. Patients with standard-risk

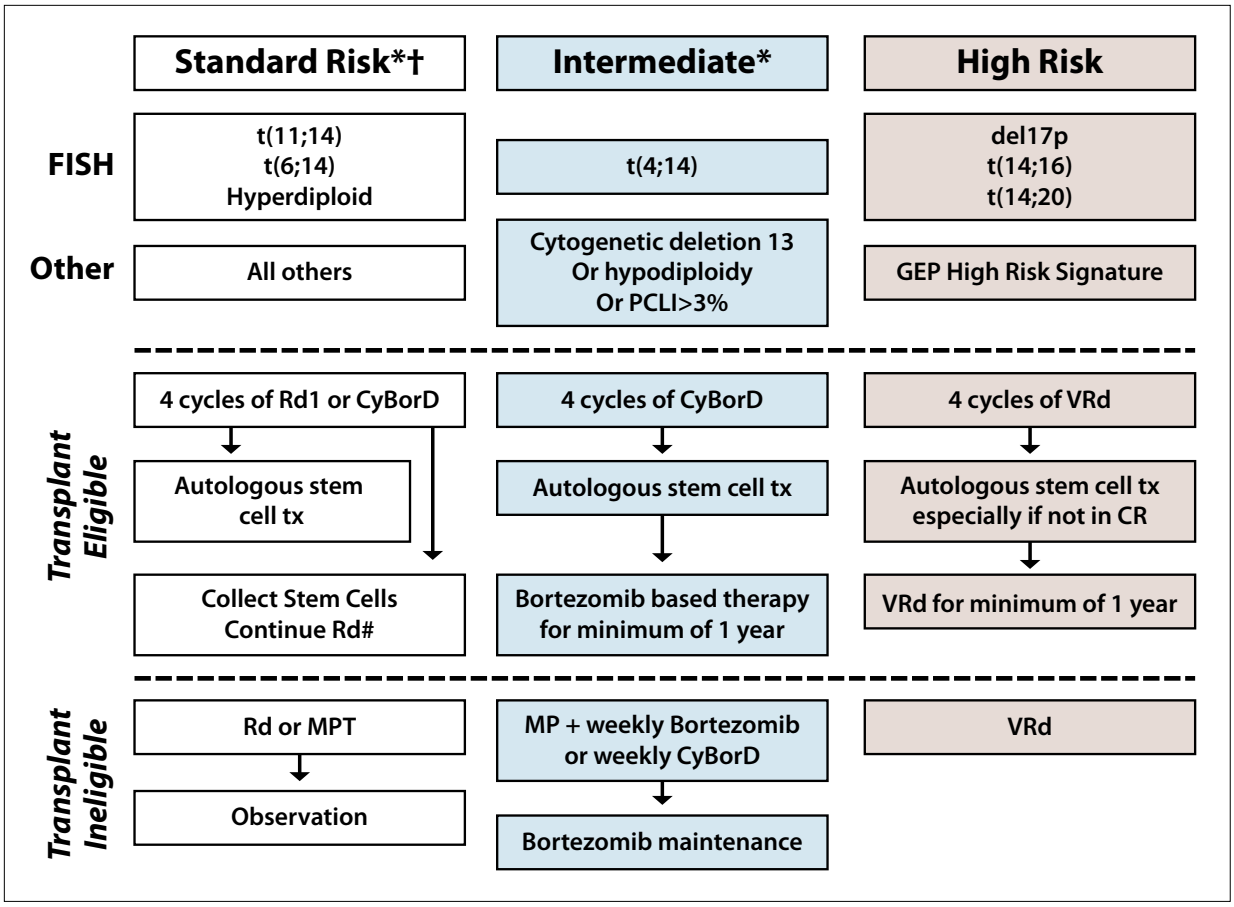

Figure 1. mSMART recommendations for a risk-adapted approach to therapy. Adapted from Chesi M, Bergsagel PL. Many multiple myelomas: making more of the molecular mayhem. *Hematology Am Soc Hematol Educ Program*. 2011;2011:344-353.
* A subset of patients with standard or intermediate risk will be classified as high-risk by GEP.
†LDH > ULN and beta-2 microglobulin > 5.5 indicate a worse prognosis.
‡Prognosis is worse when associated with high beta-2 microglobulin and anemia.
#Continuing lenalidomide is an option for patients responding to it with low toxicities; dexamethasone is usually discontinued after the first year.
CR=complete remission; CyBorD=cyclophosphamide, bortezomib, and dexamethasone; GEP=gene-expression profiling; LDH=lactate dehydrogenase; MPT=melphalan, prednisone, and thalidomide; PCLI=plasma cell labeling index; Rd=lenalidomide and dexamethasone; tx=transplant; ULN= upper limit of the normal range; VRd=bortezomib, lenalidomide, and dexamethasone.

myeloma have a median overall survival (OS) of over 8 years, whereas those with high-risk disease have a median OS of 2–3 years. Treatment approaches differ for each risk group, as detailed in Figure 1. In addition, among patients who are older and in those with a poor performance status at diagnosis, we have to be careful about potential treatment-related side effects. It is important to modify drug doses accordingly and to remain alert for infections so they may be treated right away with antibiotics or antibiotic prophylaxis. Improvements in supportive care, especially the routine use of bisphosphonates, can reduce the incidence of bony complications, which often contribute to morbidity and, indirectly, to mortality.

H&O Can you discuss your recent study on predictive factors of early mortality in multiple myeloma?

SK We must fully understand which factors contribute to early death in multiple myeloma in order to address this problem. There have not been any previous systematic studies that have looked at this issue in a clear fashion. Our finding that 10% of the patients seen at the clinic tend to die in the first year is probably an underrepresentation; many newly diagnosed patients do not actually make it to a larger center like ours.

Our study was presented at the 2011 American

Society of Hematology (ASH) meeting. We examined a cohort of patients who were seen over a 10-year period, from 1999–2008. We identified 265 patients who died within 12 months of diagnosis. For each of these patients, 2 controls were identified, each of whom had at least 12 months of follow-up, were alive at the time of last follow-up, and were closest to the deceased patient in terms of the timing of diagnosis.

Using the clinical and laboratory features, we identified parameters that best predicted for 12-month mortality. The factors that we found to be predictive of a poorer outcome within the first year included patient age greater than 72 years, International Staging System (ISS) stage III disease, Eastern Cooperative Oncology Group (ECOG) performance status greater than 2, and high levels of calcium at diagnosis. None of these factors were necessarily unexpected; the risk of death within the first year is largely driven by baseline health status and the severity of complications resulting from the disease or medications, as well as comorbidities like diabetes, high blood pressure, and poor renal function.

H&O Where should we focus our efforts for the future?

SK We must target this higher risk patient population for innovative approaches in order to improve outcome. The key is to conduct clinical trials focusing specifically on these patients, who are at risk for early death. All too often, these patients are left out of trials, and are thus not represented in treatment data. I think that the more we include these patients in clinical trials, the more we will learn about what the answers might be for treating this hidden population. Clinical trials could look at issues such as less frequent dosing, lower dosing, or therapies that are oral or subcutaneous rather than intravenous. We must discover and implement new methods that will allow these patients to minimize trips to the hospital and decrease their risk of complications.

Suggested Readings

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