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

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The Role of Autologous Stem Cell Transplant in Patients With Multiple Myeloma

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H&O What are the clinical characteristics of multiple myeloma?

JM Multiple myeloma has historically been defined by 4 clinical characteristics: elevated calcium, renal deficiency, anemia, and bone disease. These characteristics are attributable to the plasma cell disorder. They are known by the acronym CRAB. Recently, myeloma has been redefined, with the addition of 3 more clinical characteristics. The first is more than 60% plasma cells in the bone marrow. The second is elevated immunoglobulin-free light chains, in which the involved light chains are 100 times more numerous than the uninvolved light chains. The third is bone marrow that demonstrates more than 1 focal lesion on magnetic resonance imaging (MRI), as opposed to the usual diffuse pattern. I refer to the new definition as SLIMCRAB: S for 60%, Li for light chains, M for MRI, and then the historical CRAB.

H&O What factors guide management?

JM Management of myeloma has become very complex throughout the last few years. Several novel agents have been approved by the US Food and Drug Administration (FDA) and are now used in clinical practice. Therefore, instead of standard first-line, second-line, and third-line regimens, treatment is guided by disease- and patient-related factors. In general, the first major division is whether a patient is eligible for transplant. Most patients younger than 70 years with a good performance status are potential candidates for autologous stem cell transplant. Patients older than 70 years or with a poorer performance status are not candidates. When selecting additional treatments, patient-related considerations include other medical illnesses and the patient's preference for oral therapy vs intravenous or subcutaneous therapy. An important disease-related factor is risk status. We divide patients into those with higher-risk disease vs standard-risk disease, knowing that higher-risk disease requires more aggressive treatment.

H&O What are the components of risk stratification?

JM There are 4 components of risk stratification: cytogenetic features, the lactate dehydrogenase (LDH) level, elevated β_2 microglobulin, and the albumin level. Cytogenetic features essentially refer to the presence of the p53 deletion or high-risk cytogenetic abnormalities, such as translocation 4;14, translocation 14;16, and translocation 16;20. These translocations capture the majority of patients with high-risk features. There are 3 biochemical tests, for β_2 microglobulin, albumin, and LDH. The historical risk stratification and staging system for myeloma was based on levels of β_2 microglobulin and albumin; the LDH level and cytogenetic features are recent additions. This is now known as the Revised International Staging System (R-ISS).

H&O What is the goal of treatment?

JM Unfortunately, there is no cure for multiple myeloma.

In many patients, however, it has been converted from a fatal illness into a chronic one. When discussing management with my patients with multiple myeloma, I sometimes offer the analogies of diabetes or high blood pressure, which are also not curable but are controllable over the long-term. In the overwhelming majority of patients, the depth of response is an important component of long-term disease control. Most often, the goal is to dramatically reduce the burden of disease to minimize impact on the organs. This deeper remission also often translates into a longer-term remission. One of the ways to achieve a deep remission is with optimal combinations given up front followed by continuous therapy with milder treatment that allows a patient to preserve both quality of life and quantity of life by maintaining a longer remission.

H&O What are the management options?

JM There are currently 4 major pillars of myeloma care: proteasome inhibitors, immunomodulatory drugs, alkylating agents, and monoclonal antibodies. Selection among these options involves a complex decision-making process tailored to each patient. For most patients, early therapy will consist of both a proteasome inhibitor and an immunomodulatory drug. Patients who are eligible for transplant will also receive an alkylating agent, melphalan, as the conditioning regimen. We generally treat with a monoclonal antibody at the time of relapse.

The current drugs in these categories have multiple generations behind them, and they are now very effective. More than 90% of patients achieve a greater than partial remission. Among patients with standard-risk myeloma, the average survival is close to, if not exceeding, a decade. Patients with high-risk myeloma have a shortened survival, but their prognosis is also improving with the new treatments available.

H&O Which types of patients are eligible for autologous stem cell transplant, and is allogeneic transplant ever an option?

JM The first step in the care of patients with multiple myeloma is deciding whether they are eligible for an autologous stem cell transplant. In the United States, patients who are younger than 70 years and who have good performance status and organ function are generally eligible. There is strong recent evidence showing that transplant significantly contributes to the depth of response and its duration, at least among patients younger than 65 years. All patients younger than 65 years should be considered for an autologous stem cell transplant. That being said, older patients who are not eligible for transplant can still have positive outcomes with novel agents.

The role of allogeneic transplant remains limited in multiple myeloma. It is not routinely performed up front except in research protocols. It may be useful in the small group of younger patients with high-risk disease who are beginning to demonstrate rapid relapse after several therapies. We try not to save allogeneic transplant for the very end of treatment. It is considered in younger patients (younger than 60 years, if not 50 years) once they have started to demonstrate resistance to proteasome inhibitors and immunomodulatory drugs. The rationale for this approach is that allogeneic transplant still carries a high risk of significant treatment-related mortality and graft-vs-host disease, and it does not always yield substantial disease control. But in a situation in which a patient with high-risk myeloma has very limited options, it should be considered.

H&O What are the induction strategies?

JM Patients who are eligible for autologous stem cell transplant will generally receive an induction regimen consisting of a proteasome inhibitor and an immunomodulatory drug. In the United States, the most commonly used regimen is bortezomib (Velcade, Takeda), lenalidomide (Revlimid, Celgene), and dexamethasone. Other regimens, such as carfilzomib (Kyprolis, Amgen), lenalidomide, and dexamethasone, are being evaluated, especially in patients with high-risk disease or preexisting neuropathy, in whom the use of bortezomib may not be ideal.

The usual plan is to treat for approximately 4 cycles to ensure the patient demonstrates at least a partial response. We recommend that our colleagues in the community refer patients to a transplant center at the time of the second treatment cycle, so that patients can undergo evaluation before the procedure. In general, patients should not receive more than 4 cycles of lenalidomide before stem cells are collected, and they must discontinue lenalidomide for 3 to 4 weeks before the collection. It is wise to refer patients to a transplant center soon after the diagnosis, once induction therapy has been started, to ensure that the timing will be appropriate for their transplant.

H&O Is second-line induction therapy an option?

JM With induction strategies, the goal is to have a deep response. There are, however, situations in which patients have more indolent disease. Most transplant centers will want to see at least a 50% reduction in the tumor size. If this outcome is not achieved with first-line induction therapy, then second-line therapy may be considered. We tend not to go beyond second-

line treatment, so that the patient can still proceed to transplant.

H&O Is it possible to delay transplant?

JM There are some patients who would prefer to have their stem cells collected but not immediately proceed to transplant owing to their work schedule or other concerns. This treatment approach has been validated in certain studies. Generally speaking, up-front transplant is the best treatment modality. However, delaying transplant may be a reasonable option in some cases. We try not to delay transplant for high-risk patients, but it could be considered. Delaying transplant could be an option in patients who have achieved a very good response—at least a very good partial remission or a 90% reduction of their tumor with their induction regimen—and who remain on continuous therapy, usually with lenalidomide. We then consider stem cell transplant when the patient relapses for the first time. We try not to delay transplant for much longer after that. As patients grow older and the disease evolves, it may be more difficult to proceed with a stem cell transplant.

H&O What are the goals of autologous stem cell transplant?

JM Like any treatment in multiple myeloma, the goal of transplant is to reduce tumor burden to provide the patient with better quality and quantity of life. Transplant by itself can significantly improve the depth of response and contribute to its duration by virtue of a prolonged progression-free survival. Even patients who had achieved a very deep response to induction therapy, to the point of complete remission, can still benefit from transplant. These patients can remain in remission longer if they undergo transplant.

The overwhelming majority of patients who successfully complete transplant benefit from it. Few patients have very resistant disease that will relapse immediately after transplant. Recent studies, including one from the Intergroupe Francophone du Myélome/Dana-Farber Cancer Institute (IFM/DFCI), comparing induction alone vs induction plus transplant have shown a clear benefit to transplant. Transplant provides a deeper response in 10% of patients, and prolongs progression-free survival by approximately a year. Therefore, in eligible patients, we recommend transplant.

H&O Has the advent of targeted therapy in myeloma impacted the role of autologous stem cell transplant?

JM The IFM/DFCI 2009 trial was designed to help answer this question. Patients were treated with bortezomib, lenalidomide, and dexamethasone followed by lenalidomide maintenance or with bortezomib, lenalidomide, and dexamethasone followed by transplant and then lenalidomide maintenance. The goal was to isolate the role of stem cell transplant to see whether it improved outcomes. The study showed that transplant did improve outcomes, in terms of both depth of response and progression-free survival. Targeted therapy and novel agents have clearly improved the outcome of patients with myeloma. Combining these therapies with transplant can give patients the best outcome.

The advent of targeted therapies may impact the use of transplant among older patients, who may or may not be eligible for transplant. For patients in their late 60s with some comorbidities, it might be possible to avoid transplant and treat with novel agents. There are many novel agents, and patients are living longer with the disease, even if they do not undergo transplant. Transplant is associated with more toxicity in older patients, and it may be an option to treat these patients with novel agents and forgo transplant.

Disclosure

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Suggested Readings

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