

ADVANCES IN LLM

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

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The Role of Transplant in Multiple Myeloma

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H&O What is the best autologous transplant regimen for myeloma?

BB Melphalan 200 mg/m² is generally accepted to be the best preparative regimen for autologous stem cell transplantation (AutoSCT) in myeloma. Total body irradiation (TBI) has been abandoned as a preparatory autotransplant regimen for myeloma, as it was found to be more toxic than and inferior to melphalan. Not all cytotoxic agents or combination chemotherapy regimens used in the treatment of multiple myeloma (MM) require stem cell support: the highly effective DT-PACE regimen (dexamethasone and thalidomide plus 4-day continuous infusions of cisplatin, doxorubicin, cyclophosphamide, and etoposide) is hematopoietic stem cell-sparing and is frequently used as a stem cell-mobilizing regimen, with remarkable antimyeloma activity in aggressive disease.

The major dose-limiting toxicity associated with stem cell-supported standard high-dose melphalan (200 mg/m²) is mucositis, a serious problem for older patients (>70 years) and those with renal failure or with primary amyloidosis. Such patients tolerate a reduction in the dose to 140 mg/m² or 100 mg/m² quite well. A Southwest Oncology Group trial is actively accruing such patients, who are offered the option of repeated cycles (up to 3) of such intermediate-dose melphalan.

H&O When should such autotransplants be applied?

BB Although overall survival has been reported in some studies to be equivalent, whether AutoSCT was utilized as

induction, consolidation, or salvage therapy, most investigators concur that best disease control and high quality of life are assured when AutoSCT is used as part of the initial treatment strategy. Thus, in several randomized and historically controlled trials, complete remission (CR, defined by negative immunofixation analysis of serum and urine and normal bone marrow aspirate and biopsy at 2 observations done at >2 months apart) rates approach 40% or higher, particularly after “tandem” transplants involving 2 cycles of high-dose melphalan 3–6 months apart. In our Total Therapy 1 trial, initiated in 1989 and applied to 231 patients, such tandem transplants yielded 15-year overall survival and event-free survival rates of 25% and 35%, respectively. Seventeen of 87 patients (20%) have been in uninterrupted CR for 105–150 months.

H&O What applications of AutoSCT in MM would not be appropriate?

BB A last resort AutoSCT effort to treat refractory MM poses several problems. If stem cells were not obtained and cryopreserved early in a patient’s MM treatment history, they may be damaged by stem cell-toxic therapies such as prolonged standard-dose melphalan, carmustine, or local radiation. Furthermore, the benefit from late salvage transplants for patients who are refractory to almost all other treatment modalities is modest with a median survival expectation not exceeding 1.5–2 years. However, when the duration of disease control from a previous AutoSCT exceeds 3 or 4 years, we and others have successfully and safely applied second, third, and even fourth autotransplants, especially when stem cells had been procured prior to the first transplant.

H&O Is there a difference in the survival benefit associated with salvage transplantation among patients who responded to initial therapy and those who did not respond?

BB No. There is a misconception, particularly among insurance carriers, that patients should have achieved a partial remission with standard therapy in order to be a candidate for an AutoSCT with melphalan. Data exist on the equivalent outcomes among patients with primary

refractory myeloma and those responding to induction therapy. In other words, patients should not be excluded from high-dose melphalan-based AutoSCT on the basis of having failed induction therapy.

H&O What are the current outcomes associated with first-line melphalan-based AutoSCT?

BB The median survival associated with such treatment is 6–7 years, more than twice the duration observed with alkylating agents administered in standard doses. With tandem transplants, the IFM-94 trial (Attal et al. *N Engl J Med.* 2003;349:2495-2502) reported 7-year event-free and overall survival rates of 20% and 40%, respectively, thus doubling the rates obtained with a single transplant.

H&O What experimental approaches are being explored to improve on these outcomes?

BB Seeking to improve survival further, the Arkansas Total Therapy 2 study evaluated the incorporation of thalidomide (Thalomid, Celgene) into a tandem melphalan-based autotransplant regimen: 668 patients were randomized to receive or not to receive thalidomide from the inception of the 4-phase treatment program, consisting of induction therapy, tandem transplantations, consolidation chemotherapy, and maintenance. Those randomized to thalidomide had a higher CR rate (59% vs 41%) and superior 5-year event-free survival rate (54% vs 42%) compared to those on the no-thalidomide arm. With a median follow-up of 3.5 years, the overall survival is not yet different.

Our current Total Therapy 3 study evaluates the incorporation of bortezomib (Velcade, Millennium) in the upfront management of myeloma patients. Bortezomib is combined with thalidomide and dexamethasone (VTD) and added to standard PACE for induction prior to and consolidation after melphalan-based tandem autotransplants; maintenance follows with VTD in year 2 and TD (thalidomide + dexamethasone) in years 3 and 4. Thus far, 200 of the eventual target of 300 patients have been enrolled; among some 150 presently evaluable patients, the current estimated frequency of CR + nodal CR exceeds 80%. Importantly, both transplants were completed within 6 months after start of protocol in the majority of patients compared to 12 months in the Total Therapy 2 study, due to reducing induction and consolidation cycles from 4 to 2. Since CR is the best currently available surrogate for long-term disease control, the progressive increase in CR rate from 40% with Total Therapy 1 to approximately 60% with Total Therapy 2 plus thalidomide, to the so-far higher CR rate with Total Therapy 3 bodes well for further extension of event-free and overall survival from that observed with Total Therapy 2.

Current debates concern the exclusively front-line use of newer agents such as thalidomide, its analog lenalidomide (Revlimid, Celgene), and bortezomib plus dexamethasone (reserving transplantation for later once disease relapse occurs) as opposed to their use as induction prior to or maintenance after AutoSCT. Pilot first-line studies with TD, VTD, and lenalidomide + dexamethasone have effected CR rates up to 20–30%, especially with the VTD regimen. Since many patients have been subsequently transplanted, no data are available to judge the durability of remissions induced by these newer agents. Preliminary data suggest, however, that relapses occur rather promptly upon cessation of therapy with these agents, which may be necessitated by severe neuropathy or other toxicities. This contrasts with typically durable remissions after high-dose melphalan in the two thirds of patients lacking cytogenetic abnormalities.

The appeal of these new agents is based on their targeting of defined (albeit often multiple) pathways. It is quite amazing that, to date, no serious efforts have been devoted to understanding the molecular signaling pathways conferring melphalan-induced apoptosis or resistance. Because AutoSCTs have benefited many thousands of patients worldwide afflicted with myeloma, doubling patient survival, the use of the AutoSCT modality should not be neglected. Some new agents, such as bortezomib and thalidomide, can cause debilitating peripheral neuropathy after prolonged administration, warranting thoughtful use of all currently active drugs, including melphalan, with AutoSCT for optimal myeloma management with the prospect of effecting lasting remissions while minimizing long-term toxicities.

In my estimation, patients with aggressive myeloma, best identified by cytogenetic abnormalities detectable by traditional laboratory tests, are the most appropriate population in which to study new approaches. If durable responses beyond 3 years can be achieved, true progress will have been made.

H&O What is the role for allogeneic transplantation in the treatment of MM?

BB Donor lymphocytes can exert a very powerful graft-versus-myeloma effect. For example, at our institution, a patient who was refractory to several AutoSCTs underwent an AlloSCT from an unrelated donor. The graft was initially purged of donor T cells. The patient did not respond to a highly myeloablative regimen with TBI and combination chemotherapy, but achieved a CR within weeks of lymphocyte infusion. High transplant-related mortality (exceeding 40%) has led most investigators to abandon this approach in favor of so-called mini-allogeneic or nonmyeloablative transplants with

low-dose TBI or melphalan at 100–140 mg/m² with or without fludarabine as a conditioning regimen. The 1-year mortality rate could be reduced to 10–15%, especially when mini-allotransplantation is performed while the patient is in a remission safely obtained through AutoSCT within the preceding 6 months. Unfortunately, however, such tandem auto-/mini-allotransplant approach does not seem to effect durable disease control in high-risk patients presenting with abnormal cytogenetics.

H&O What are the future directions regarding the role of transplant in multiple myeloma?

BB Investigators in the field of MM research need to find ways to skillfully apply the various modalities now available, incorporating new agents without abandoning AutoSCT. Ongoing clinical trials are evaluating new agents as maintenance therapy after transplantation and as induction therapy prior to transplantation. At our institution we are evaluating the incorporation of newer agents before and after transplantation in high-risk patients. The Southwest Oncology Group and other US as well as international cooperative groups are conducting standard-dose

trials with thalidomide or lenalidomide + dexamethasone, as well as combination therapies of these new agents together with standard cytotoxic drugs (eg, bortezomib/doxorubicin/dexamethasone and melphalan/prednisone/thalidomide). Remarkably high CR rates approaching 30–40% have been observed, but it is too soon to know whether these responses are durable.

Suggested Reading

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