

Blood, 15 May 2004, Vol. 103, No. 10, pp. 3612-3613.

High-dose therapy for amyloidosis: the end of the beginning?

The perception that the outcome of AL amyloidosis patients subjected to high-dose chemotherapy and autotransplantation is superior to the disappointing fate of those treated conventionally¹ was questioned by a retrospective study from the Mayo Clinic suggesting that eligibility for transplantation was responsible for the difference to a significant extent.² However, evidence supporting the benefit of high-dose therapy in amyloidosis is compelling, despite not being comparative.³ This includes the achievement of complete hematologic remissions in a substantial proportion of patients, and improvement in amyloid-induced organ dysfunction in many^{1,3}—phenomena that are rare with conventional treatment. In a comprehensive report on autografts in amyloidosis,³ the Boston University group has shown that patients receiving a higher dose of melphalan (200 mg/m² rather than 140 mg/m²) for conditioning had higher response rates and better survival. This dose-response relationship lends further support to the usefulness of autotransplantation in amyloidosis.

In a retrospective case-control study, Dispenzieri and colleagues (page 3960) show that the survival of amyloidosis patients subjected to high-dose therapy was significantly superior to those with similar biologic features treated conventionally. The median survival of patients treated conventionally was less than 3 years, whereas the median had not been reached for autografted patients at 4 years, with 71% projected to be alive. This difference is even more remarkable considering the fact that almost half of the patients who underwent transplantation received conditioning regimens that would now be considered suboptimal. The 13% transplantation-related mortality, identical to that reported from Boston University,³ while substantially lower than that reported historically,¹ is still much higher than what is seen with autotransplantation for other diseases, suggesting that these transplantations should perhaps be confined to centers with significant experience in plasma cell dyscrasias.

The data from the Mayo Clinic and Boston University are impressive enough to make a prospective, randomized study of high-versus conventional-dose therapy in amyloidosis scientifically unattractive and practically impossible. And yet, questions remain.

Is pretransplantation induction therapy required? Not with melphalan-prednisone.⁴ However, the role of dexamethasone has not been determined. This may be reasonable in selected patients (eg, those with rapidly increasing proteinuria).

Can autografts be made safer, particularly with 200 mg/m² melphalan? The role of cytoprotective agents such as amifostine remains to be determined.

Should maintenance therapy with corticosteroids or interferon be given after transplantation to increase the hematologic response rate and improve its durability? We have now started seeing hematologic relapses that are followed by progressive amyloidosis, suggesting that strategies to delay recurrence, as used in myeloma, may be worthwhile.

How should recurrent disease be treated? Should another autograft be considered as salvage therapy—particularly in patients not receiving the full dose of melphalan for the first autograft? Is there a place for allogeneic hematopoietic stem cell transplantation in selected patients, bearing in mind increased toxicity due to organ dysfunction?² What is the place of novel agents such as bortezomib and thalidomide?

Now that we have agreed upon the utility of high-dose therapy in amyloidosis, perhaps we can move on to addressing the other questions.

— **Jayesh Mehta**

The Robert H. Lurie Comprehensive Cancer Center of Northwestern University

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