Comment on Bladé et al, page 3755

To transplant or not to transplant?

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In this issue of Blood, Bladé and colleagues report that HDT does not improve overall or event-free survival in patients responding to initial chemotherapy.

Use of high-dose melphalan with stem cell transplantation is a major advance in the therapy of multiple myeloma (MM). To date, 5 randomized studies have compared the outcomes of patients treated with high-dose therapy (HDT) versus standard-dose therapy (SDT). The Intergroupe Francais du Myelome 90 (IFM90)1 and the Medical Research Council (MRC) VII trials show statistically significant increased complete response (CR) rates, with prolonged event-free survival (EFS) and overall survival (OS), in the patient cohorts receiving HDT. In contrast, the Myelome-Autogreffe Group (MAG) study does not show superiority of HDT for EFS and OS;2 and the US Intergroup trial, which randomized patients to HDT versus SDT with delayed HDT at relapse, does not show superiority of HDT for either achievement of CR (17% vs 15%) or prolongation of OS (58 vs 53 months).3

The study by Bladé and colleagues published in this issue of Blood, the fifth study comparing HDT versus SDT, shows significantly higher CR rates after HDT (30% versus 11%), without statistically significant improvement in progression-free survival (PFS; 42 versus 33 months) and OS (61 versus 66 months). Since only 12% patients in the SDT cohort received HDT as salvage and survival after relapse in both arms was equivalent (15.9 versus 16.4 months), the lack of OS benefit of HDT cannot be due to salvage transplants in the conventional dose therapy arm. This report differs from prior randomized trials, since only patients responding to initial therapy were eligible for randomization. A prior retrospective study of patients who were candidates for, but did not receive, HDT also supports equivalent patient outcomes with SDT.5

Who benefits from HDT? In this study, increased CR rate does not translate into a survival benefit; to date, a clear benefit of HDT is observed only in those randomized with significantly lower CR rates after SDT, supporting the view that achieving higher CR rates is associated with prolonged survival. Novel therapies like thalidomide, bortezomib, and lenalidomide (Revlimid) with activity in relapsed refractory MM are now being used as initial therapy to achieve higher frequency of CR and may thereby improve outcome. Nonetheless, 6 of 9 patients in this study who were unresponsive to initial therapy underwent HDT and achieved partial response (PR), suggesting that HDT can achieve responses even in patients with primary refractory disease.

Although 3 of 5 randomized studies show that HDT achieves prolongation of EFS and OS ranging from 4 to 12 months and from 1 to less than 23 months, respectively, few, if any, patients are cured. In the current study, no benefit in either EFS or OS is observed after HDT. Given these modest benefits, it is critical to assess quality of life achieved after HDT; indeed, a single study has shown that quality of life was inferior at 6 months after HDT than SDT.6

Two major strategies are under evaluation to improve outcome after HDT. First, repeated or tandem HDT has improved PFS.
and OS in some studies, with benefit of second HDT especially for those who do not achieve CR or near CR after single HDT. Second, attempts are under way integrating novel agents such as thalidomide, bortezomib, and lenalidomide into the transplantation paradigm not only to enhance response before HDT, but also as maintenance therapies to prolong PFS and OS after transplantation. Novel agents therefore may improve outcome and ultimately obviate the need for HDT.

REFERENCES


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