

## Tandem Transplants in the Treatment of Multiple Myeloma

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Based on the experience in acute leukemias, where achievement of complete remission is a *sine qua non* for long-term survival and cure, the management of multiple myeloma (MM) patients has shifted from a palliative approach in the late 1980s to a potentially curative approach today. Encouraged by the success of early trials,<sup>1</sup> in which true complete remissions were induced by escalation of the melphalan (Alkeran, GlaxoSmithKline) to 100–140 mg/m<sup>2</sup>, investigators sought to further increase the complete remission rate by using even higher doses of melphalan (200 mg/m<sup>2</sup>) in combination with stem cell support. Application of melphalan-based tandem autotransplants with a curative intent was first tested by our group at the University of Arkansas (Total Therapy I [TT I] trial) in newly diagnosed or minimally pretreated patients. One and 2 courses of high-dose therapy (HDT) were given to 84% and 71% of patients, respectively. An incremental improvement in complete remission rate from 26% after 1 transplant to 38% after 2 transplants on an intent-to-treat analysis was observed (from 32% to 48% for patients who actually completed the intended treatment). The median event-free survival (EFS) and overall survival (OS) were 43 months and 68 months, respectively.<sup>2</sup> A better outcome was seen in the absence of an abnormal karyotype. With a median follow-up of 9.5 years, the 10-year OS was 43% in the absence of abnormal cytogenetics (two thirds of patients) versus 10% with abnormal cytogenetics ( $P < .001$ ).

Intensification of TT I (more intensive induction, intensive posttransplant consolidation chemotherapy, and more post-transplant dexamethasone [Decadron, Merck]) is currently being studied in the TT II trial (in which patients are also randomized to receive upfront versus no upfront thalidomide [Thalomid, Celgene]). A comparison of outcome of the first 231 patients in the TT II study (median follow-up, 3 years) versus the 231 patients in the TT I study revealed

significantly better 4-year OS (80% vs 64%;  $P = .01$ ) for TT II patients without baseline cytogenetic abnormalities.<sup>3</sup>

Several European groups adopted the tandem autotransplants approach. The Intergroupe Francophone du Myelome (IFM)-94 conducted a randomized trial testing 1 (melphalan/total body irradiation [TBI]) versus 2 (melphalan followed by melphalan/TBI) transplants; with a median follow-up of 5 years. The median OS and the 7-year survival were superior in the tandem versus the single transplant arm (50 months vs 31 months;  $P = .02$ , and 42% vs 21%;  $P = .01$ , respectively). The OS curve separated only after 3 years of follow-up. Patients who achieved less than a near complete remission after the first transplant appeared to benefit the most from tandem transplants.<sup>4</sup>

The Spanish Grupo Español de Linfomas y Trasplante de Médula Ósea (GELTAMO) evaluated tandem transplants in a phase II trial of 88 patients. An incremental improvement in complete remission rate (30% after the first transplant with melphalan to 48% after the second transplant with cyclophosphamide [Cytosan, Bristol-Myers Squibb], etoposide [VePesid, Bristol-Myers Squibb], carmustine [BCNU, Bristol-Myers Squibb]) was seen, confirming the findings of the TT I trial. Although no differences in outcome were detected between patients achieving complete remission after 1 or 2 transplants, (median OS: 68 months and 72 months, respectively;  $P = .8$ ), having attained complete remission after the second transplant was the most important prognostic factor for OS and EFS ( $P = .00001$ ).<sup>5</sup>

The Dutch-Belgian Hemato-Oncology Cooperative Group (HOVON) study compared tandem intermediate-dose melphalan (70 mg/m<sup>2</sup>) without stem cell support with the same regimen followed by 1 transplant (TBI, cyclophosphamide). Despite a higher complete remission rate and longer time to progression in the transplant arm, OS was not different (50 months vs 47 months) in the 2 arms.<sup>6</sup> However, the follow-up time in the study was short (median, 33 months), and the use of a TBI-based conditioning regimen may have affected the outcome, as at least 3 studies, 1 of which was randomized, have suggested that TBI-based regimens are inferior to melphalan alone.<sup>7-9</sup>

Two European randomized studies, reported in abstract form, compared 1 versus 2 transplants in MM patients. Cavo et al<sup>10</sup> reported the results of the Italian “Bologna 96” trial, which tested 1 (melphalan) versus 2 (melphalan followed by melphalan/busulfan [Busulfex, Orphan]) transplants. A statistically significant superior EFS for the 2 transplants arm

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has already been detected. With a median follow-up of only 38 months, no difference in OS has yet been observed. The Myelome-Autogreffe Groupe trial 95 tested 1 (carmustine/melphalan/etoposide/cyclophosphamide/TBI) versus 2 (melphalan followed by melphalan/etoposide/TBI) transplants. After a median follow-up of only 27 months, no difference in EFS and OS between the arms has been observed.<sup>11</sup>

We consider it premature to conclude that patients in complete remission after 1 transplant will not benefit from a second autotransplant. Patients who achieve complete remission after 1 transplant are extremely sensitive to chemotherapy and theoretically should be the group likely to benefit the most from a second transplant. That the majority of patients (even those without any cytogenetic abnormalities) eventually relapse signifies that very few patients are overtreated with tandem transplants. The current evidence, combined with extremely low transplant-related mortality in specialized centers and the almost negligible risk of secondary myelodysplasia in patients not exposed to prolonged conventional treatment,<sup>12</sup> makes us strong supporters of the tandem transplant approach, especially in patients with low-risk disease features, that is, normal cytogenetics, 40% of whom are alive 10 years after transplant. Further progress will hopefully come from a skillful combination of tandem transplants with novel drugs targeting the bone marrow microenvironment, which plays a major role in MM drug resistance.<sup>13</sup> Nonmyeloablative allogeneic transplant<sup>14</sup> and novel strategies (such as dendritic cell vaccination) should be offered to high-risk patients in whom even the timely application of tandem transplants appears not to be curative.

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## CON

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The use of conventional-dose melphalan and prednisone (MP) has prolonged OS to 48 months in MM patients in whom disease either responds or stabilizes; only those patients who progressed had inferior survival (15 months).<sup>1</sup> Although nearly 10,000 patients have been treated in trials comparing MP with combination chemotherapy, patient outcome has not been significantly improved despite more rapid achievement of response in some studies in the combination chemotherapy arm.<sup>2</sup>

Two important developments have changed therapeutic approaches in MM. First, high-dose melphalan with stem cell transplant has been found to increase the rates of complete response (CR) and OS. To date, 5 randomized studies have compared the outcome of patients treated with HDT versus standard-dose therapy. The IFM-90<sup>3</sup> and the Medical Research Council (MRC)-VII trials<sup>4</sup> have demonstrated statistically significantly improved CR rates, EFS, and OS in the cohort receiving HDT. In contrast, the Spanish Program for the Study and Treatment of Malignant Hemopathies (PETHEMA) trial<sup>5</sup> showed significant improvement in CR with HDT, without a statistically significant effect on EFS or OS, and a study by Fermand et al<sup>6</sup> similarly failed to show superiority of HDT for EFS and OS. A recent US intergroup study<sup>7</sup> in which patients were randomized to receive either HDT or conventional-dose therapy followed by delayed HDT at relapse did not find a statistically significant improvement with HDT in either CR (17% vs 15%) or OS (58 months vs 53 months). In this study, 52% of 161 patients failing conventional therapy received HDT as salvage therapy. These patients experienced a response rate of 59%. Survival after relapse was 30 months, compared with 23 months for those not receiving salvage HDT ( $P=.05$ ). Fermand and colleagues also examined the timing of HDT and found superior CR rates (19% vs 5%) in patients who underwent HDT after induction treatment (early) versus

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patients who received HDT as salvage for relapse after conventional treatment (late). OS was equivalent (65 months vs 64 months), but EFS (39 months vs 13 months) and time without symptoms and toxicity (28 months vs 22 months) favored the early transplant approach. Table 1 summarizes response and survival rates from these trials.

**Table 1.** Response and Survival Rates in Studies Comparing HDT and CT in Newly Diagnosed MM

Study	Therapy	Patients, n	CR, %	Improvement in EFS	Improvement in OS
Attal et al <sup>3</sup>	CT HDT	100 100	5 21*	9*	>23*
Child et al <sup>4</sup>	CT HDT	200 201	9 44*	12*	12*
Blade et al <sup>5</sup>	CT HDT	83 81	11 30*	8	5
Ferland et al <sup>6</sup>	CT HDT	96 94	— —	5	5
Barlogie et al <sup>7</sup>	CT HDT	252 258	15 17	4*	5

\*Statistically significant difference.

HDT=high-dose therapy with autologous transplantation; CT=combination chemotherapy; MM=multiple myeloma; CR=complete response; EFS=event-free survival; OS=overall survival.

Although 3 of 5 studies showed a benefit for HDT, the duration of benefit after HDT remains limited. As seen in Table 1, the improvements in EFS and OS after HDT versus conventional-dose therapy have ranged from 4 months to 12 months and from 1 month to >23 months, respectively. Therefore, it is important to identify the extent and quality of the benefit achieved with HDT; whether HDT leads to improved quality of life remains unclear. In one study, patients receiving HDT spent more time in the hospital in the first 6 months after HDT than patients treated with conventional chemotherapy treatment arm. In the same study there was a trend for reduction in pain and fatigue in HDT recipients at 36 months after transplant, but no statistically significant difference.

With the demonstration that single HDT confers a modest survival benefit, several randomized trials have examined a single versus double HDT approach. A recent study by Attal and colleagues<sup>15</sup> found no difference in response rate or CR rates in recipients of single versus double HDT, but did show a statistically significant improvement in predicted 7-year EFS and OS in the double HDT cohort. Although the original hypothesis of administering a second transplant was that patients with the most responsive disease would benefit from the second transplant, this study in fact showed the opposite to be the case. Specifically, those patients who did not achieve a CR or a very good partial response after the first HDT achieved a significantly improved response and survival after a second HDT treatment compared to patients who were not randomized to second HDT. The study findings confirm the importance of CR, suggesting that those who achieve CR after single HDT may not benefit from a second HDT. Ferland and colleagues have compared single HDT followed by a second HDT as initial therapy (early) versus salvage for relapse after first HDT (late), and found no difference in outcome. Neither the

Dutch-Belgian HOVON trial (N = 373) (Segeren et al. *Blood*. 2001) nor the “Bologna-96” (N = 220) trial (Cavo et al. *Blood*. 2002), with median follow-up times of 27–30 months, have yet shown significant benefits for tandem transplantation.

The second recent advance in therapeutic strategies has been the identification of novel therapies targeting the myeloma cells and the microenvironment including thalidomide, CC-5013 (Revimid/RevLimid, Celgene), and bortezomib (Velcade, Millennium).<sup>8</sup> In preclinical models, these agents have been shown to overcome conventional drug resistance. Specifically, thalidomide achieves responses in patients with relapsed, refractory MM. More than 50% of patients who do not respond to either dexamethasone or thalidomide alone respond to these agents in combination. In clinical trials treating patients with relapsed and relapsed/refractory myeloma, including many patients who have received HDT, both bortezomib and CC-5013 have achieved responses, including CRs, in about one third of patients, and a stable disease or better has been observed in up to 75% of patients.<sup>9,10</sup> These agents are now being evaluated as initial therapy, alone and in combination with conventional therapies, with preliminary evidence of high overall response and CR rates. Weber et al<sup>11</sup> reported a response rate of 72% (16% CR) for newly diagnosed MM patients treated with thalidomide and dexamethasone. In a study by Palumbo et al,<sup>13</sup> melphalan, prednisone, and thalidomide achieved a CR rate of 22%.<sup>12</sup> Pegylated doxorubicin, vincristine, reduced frequency dexamethasone and thalidomide combination therapy has been shown to achieve a CR or near CR rate of 46%, and the combination of bortezomib, thalidomide and dexamethasone has been shown to achieve a 22% CR or near CR rate.<sup>14</sup> These CR rates are in the range observed with HDT. In addition, these agents are now being evaluated in the transplant setting in an attempt to prolong EFS after single HDT. Preliminary studies show that thalidomide given after transplant is well tolerated at doses <200 mg/day, with in vivo induction of natural killer cells. Due to its activity in advanced disease coupled with its oral bioavailability and favorable tolerability profile, CC-5013 may be effective as maintenance therapy after HDT and is currently being evaluated in this setting.

HDT may not be superior when compared to newer agents that achieve higher CR rates than standard dose therapies. An important question therefore is whether patients achieving a CR or near CR after treatment with combinations of novel and conventional therapies will benefit from consolidation with HDT. In IFM-94,<sup>15</sup> the patients who had achieved the best responses after single HDT did not benefit from a second HDT. It is possible that patients who respond well to combination therapy with standard and novel agents may experience a limited benefit from HDT.

In conclusion, single HDT confers a modest benefit over conventional chemotherapy in terms of EFS and OS, and cures few, if any, patients with MM. A second HDT and therapy with novel agents are 2 approaches to improve outcome that should be evaluated in clinical protocols. Future research should include evaluation of combination therapy with both novel and conventional agents, based upon preclinical rationale, and integration of these agents into trans-

plantation approaches. Ultimately, the use of novel agents early in the management of myeloma may achieve high CR rates and alleviate the need for HDT.

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