Role of Bone Marrow Transplantation in the Disease Pathway of Myeloma

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Transplantation (ASCT) compared with conventional chemotherapy, ASCT has become standard care, at least for younger patients (up to age 65 years) without renal failure. However, ASCT is being challenged again by the introduction of novel agents such as bortezomib, thalidomide, and lenalidomide.

In the allogeneic setting, the immunologic effect of donor’s lymphoid cells, the so-called graft-versus-myeloma effect, explains some long remissions and possible cures. However, the major issue is transplant-related mortality mostly related to conditioning regimen toxicity and to graft-versus-host disease. Reduced-intensity conditioning allogeneic stem cell transplantation (SCT) was developed with the goal of reducing transplant-related mortality while harnessing the graft-versus-myeloma effect.

ASCT

ASCT Versus Conventional Chemotherapy

Two randomized studies from France and the United Kingdom showed that ASCT is superior to conventional chemotherapy in response rate, event-free survival (EFS), and overall survival. Moreover, combinations of conventional chemotherapy with novel agents such as thalidomide or bortezomib yield CR rates and EFS comparable to those achieved with standard single ASCT. Prospective randomized studies are needed to evaluate the impact of novel agents versus or in combination with ASCT. Myeloablative conditioning regimens before allogeneic stem cell transplantation are being replaced with concurrent autologous-transplantation and reduced-intensity conditioning allogeneic stem cell transplantation. Transplant-related mortality associated with this procedure is lower, but more follow-up is needed before definite conclusions can be drawn. (JNCCN 2007;5:163–169)
However, 2 recent publications raised concerns because of the lack of significant benefit from ASCT compared with conventional chemotherapy. In the first one from Spain, only patients whose disease responded to initial chemotherapy were randomized to undergo treatment with ASCT or further conventional chemotherapy. Although the CR rate was significantly higher in the ASCT arm (50% vs. 11%), no difference was seen in EFS and OS. Compared with other randomized studies where randomization occurred at diagnosis, the design of this trial introduced a selection bias, and only 75% of the patients entering the study were randomized. This fact could be important because ASCT is a useful salvage treatment for patients with primary refractory multiple myeloma. Moreover, although no significant difference was seen in progression-free survival between ASCT and conventional chemotherapy, the median progression-free survival was better in the ASCT arm (42 months vs. 33 months). With more patients, this difference might have become significant.

In a large Intergroup trial in the United States, 516 patients up to age 70 years were randomized between conventional chemotherapy and ASCT after undergoing induction therapy with vincristine, doxorubicin, and dexamethasone (VAD). This trial also had a selection bias: 813 newly diagnosed patients were registered and assigned to receive 4 cycles of VAD followed by stem cell collection and randomization to transplantation or vincristine/carmustine/melphalan/cyclophosphamide/prednisolone. Only 516 were randomized and, of these, only 424 actually underwent the assigned therapy. No difference in response rate, progression-free survival, and OS was seen between the groups. One important distinction between the United States trial and the French and United Kingdom trials is that a significant proportion of patients in the conventional chemotherapy arm underwent autologous transplantation as salvage therapy when they experienced primary refractory disease or relapse. Another explanation is that, although results achieved with ASCT in this trial are comparable to those achieved in the others, results seen with conventional chemotherapy are much better, as shown in Table 1.

However, similar to the Spanish study, patients were randomized only after undergoing induction conventional chemotherapy, and only 63% of patients who entered the study were actually randomized, which may again represent a selection bias.

The following conclusions can be drawn from these randomized studies:

- ASCT should not only be offered only to patients experiencing response to their initial chemotherapy but also to patients with primary refractory multiple myeloma.
- ASCT improves the outcome mostly by increasing the CR + VGPR rate.
- ASCT is superior to standard conventional chemotherapy, but when results of conventional chemotherapy are improved, the benefit of ASCT is no more significant.

However, comparing conventional chemotherapy with ASCT is no longer a relevant question, because results of ASCT have already improved compared with those achieved in the 1990s. Two different approaches have contributed to this improvement in the past few years: further dose intensification and introduction of novel agents.

Further Dose Intensification

The first step in improving results of ASCT was the introduction of double-intensive therapy, with the objective of increasing the CR rate. The Arkansas group developed a double ASCT program for newly diagnosed patients and those experiencing relapse.

In newly diagnosed patients, the CR rate increased at each step of the procedure. This better tumor cell reduction translated to encouraging median EFS and OS of 43 months and 68 months, respectively.

The InterGroupe Francophone du Myelome (IFM) was the first to conduct a randomized trial comparing simple and double ASCT in 399 patients up to 60 years of age. The 7-year EFS and OS were significantly improved in the double ASCT arm (20% vs. 10% and 42% vs. 21%, respectively). The updated results of a Dutch study and the preliminary results of 3 other randomized studies also favor double ASCT.

The IFM 94 trial confirmed the feasibility of double ASCT because 75% of patients underwent the second ASCT, and the toxic death rate was less than 5%. However, many investigators considered the benefit of this approach to be marginal and were concerned by the cost and morbidity. Therefore, defining which patients benefitted more from this aggressive management seemed important. In the IFM 94 trial, the only parameter to define patients who did not benefit from double ASCT was response to the first ASCT. Patients with less than 90% reduction of their...
M-component after 1 ASCT had a longer OS in the double ASCT arm, whereas patients experiencing CR of VGPR after the first ASCT had the same OS with or without the second.

In the Arkansas and IFM experiences, patients with favorable prognostic factors (low $\beta_2$-microglobulin or high albumin levels, no cytogenetics abnormalities) could experience very long remissions, whereas patients with high $\beta_2$-microglobulin level or cytogenetic abnormalities experienced a poor-prognosis event with double ASCT.\textsuperscript{14–16} To further improve results of double ASCT, Barlogie et al.\textsuperscript{17} evaluated a more intensive regimen called Total Therapy 2 with 4 consecutive phases: 1) increased-intensity induction treatment (including combination chemotherapy with dexamethasone, cyclophosphamide, etoposide, and platinum); 2) tandem ASCT; 3) consolidation chemotherapy; 4) and maintenance with interferon and dexamethasone. In this trial, patients were randomized to either receive or not receive thalidomide from initiation of treatment. Comparison of 345 patients in the Total Therapy 2 arm who were not treated with thalidomide, and 231 patients previously treated with the Total Therapy 1 program showed that although the CR rates were identical (43% vs. 41%), the 5-year probability of continuous CR (45% vs. 32%; $P < .001$) and 5-year EFS (43% vs. 28%; $P < .001$) were superior in the Total Therapy 2 program. This was translated into a trend for improved OS (62% vs. 57%; $P = .11$). Although not randomized, this comparison favors the more intensive regimen, and particularly post-ASCT consolidation. The IFM also proposed a more intensive regimen in the IFM 99 trial, but only for patients with poor-risk factors (high $\beta_2$-microglobulin level + del 13 using fluorescence in situ hybridization [FISH] analysis).\textsuperscript{18} This subgroup of 219 patients underwent double ASCT with an increased dose of melphalan (220 mg/m$^2$) before the second procedure. The CR + VGPR rate increased from 34% after 1 ASCT to 51% after 2 ASCTs, which translated into encouraging median EFS and OS (30 and 41 months), respectively. These results seemed to be superior to those achieved previously in high-risk patients.

### Novel Agents in Combination with ASCT

The second way to improve results of ASCT is to use novel agents.\textsuperscript{14–16, 18} The impact of adding thalidomide to a double ASCT program was evaluated in the randomized Total Therapy 2 program.\textsuperscript{19} In this study, 323 patients were randomly assigned to receive thalidomide from the onset until disease progression or adverse effects occurred and 345 patients did not undergo treatment with thalidomide. The thalidomide arm showed a significantly superior CR (62% vs. 43%; $P < .001$) and better 5-year EFS rates (56% vs. 41%; $P = .01$). However, no difference was seen in the 5-year OS (65% in both groups) because of a shorter survival after relapse (median 1.1 vs. 2.7 years; $P = .001$). Relapses experienced by patients in the thalidomide arm seemed to be more resistant than those experienced by patients in the control arm. Moreover, the combination of chemotherapy and thalidomide during induction treatment induced a high incidence of deep vein thrombosis (30%), and a peripheral neuropathy grade greater than 2 was observed in 27% of patients.
This study shows the potential interest of adding thalidomide, but also raises the issue of the optimal dose and duration of treatment, because thalidomide used as continuous adjunctive therapy to the very intensive Total Therapy 2 regimen did not confer a survival benefit. In the IFM 99-02 trial, thalidomide was evaluated as maintenance therapy after double ASCT in patients younger than 65 years with standard prognosis (0 or 1 adverse prognostic factors defined as \( \beta_2 \)-microglobulin > 3 mg/L or del 13 using FISH analysis). \(^{20}\) In this 3-arm study, 597 patients experiencing response to double ASCT were randomly assigned to undergo no further treatment or treatment with pamidronate or pamidronate plus thalidomide (up to 400 mg/d).

The 3-year EFS was 52% in the thalidomide arm versus 36% in the control arm and 37% in the pamidronate arm, which translated to a longer 4-year OS (87% in the thalidomide arm vs. 77% and 74% in the other 2 arms). However, the benefit was significant only in patients who had not experienced CR or VGPR after the second ASCT, and was therefore mostly caused by an increase of the CR + VGPR (from 50% after 2 ASCTs to 68%). Although deep vein thrombosis was rare (2%) because of the use of thalidomide alone, peripheral neuropathy was noted in 68% of patients and was the main reason for drug discontinuation. The median dose of thalidomide in this study was 200 mg/d and the median duration of treatment was 15 months.

The difference in OS benefit between these 2 studies raises the issue of potential risks associated with long-term treatment with thalidomide. The optimal daily dosage and optimal duration of maintenance treatment with thalidomide must be further evaluated. Lenalidomide and bortezomib are currently being evaluated in this setting.

Novel agents could also be used as part of induction treatment before ASCT. In the United States, the combination of thalidomide plus dexamethasone has already replaced dexamethasone alone or combined with chemotherapy, such as in the VAD regimen, and has recently been approved by the U.S. Food and Drug Administration. This approval is partly based on the results of a randomized study showing that thalidomide + dexamethasone yielded more responses than thalidomide alone, but at the expense of greater toxicity. \(^{21}\)

In a retrospective analysis, the overall response rate achieved with thalidomide plus dexamethasone was also superior to that achieved with VAD. \(^{22}\) However, in both studies, the CR rate was not superior in the thalidomide/dexamethasone group. Whether the higher remission rate will translate into a higher post-ASCT CR rate and a longer remission is still unknown. Moreover, the increased incidence of deep vein thrombosis in the patients treated with thalidomide was a concern. \(^{21,22}\)

Several phase II trials have also evaluated the impact of bortezomib given before ASCT in combination with dexamethasone or chemotherapy. \(^{23-25}\) Preliminary results are encouraging regarding efficacy and safety; because high CR rates are achieved and stem cell collection is feasible, these combinations are currently tested before ASCT in randomized trials. The combination of lenalidomide with dexamethasone is also an attractive induction regimen. \(^{26}\)

**ASCT in Older Patients**

ASCT is feasible in patients aged 65 years and older, \(^{27}\) but the issue of selection bias should be raised in non-randomized studies. The usual conditioning regimen of melphalan 200 mg/m\(^2\) is probably too toxic, particularly in patients older than 70 years. \(^{28}\) An Italian group proposed 2 to 3 courses of intermediate-dose melphalan (100 mg/m\(^2\)) supported by ASCT. After showing the feasibility of this approach, \(^{29}\) they performed a randomized study comparing this approach with conventional chemotherapy involving melphalan-prednisone (MP) in patients aged 50 to 70 years. \(^{30}\) Intermediate-dose melphalan was superior to MP even in the subgroup of patients aged 65 to 70 years. However, in the IFM 9906 trial, the same regimen was compared with MP and MP plus thalidomide (MPT) in patients aged 65 to 75 years. \(^{31}\) Although the CR-VGPR rate achieved with 2 courses of melphalan, 100 mg/m\(^2\), was comparable to that achieved with MPT (43% vs. 50%) and dramatically superior to MP (8%), relapses were rapid. Median progression-free survival was not significantly different between MP and melphalan 100 mg/m\(^2\), and was clearly inferior to MPT. One possible explanation for this discrepancy between the Italian and French studies is that maintenance therapy with interferon plus dexamethasone was administered in the Italian study. \(^{30,31}\) However, results of the IFM study do not support the use of ASCT in older patients outside a clinical trial. \(^{31}\)
Are Novel Agents Going to Replace ASCT?
Palumbo et al.\textsuperscript{32} also compared MP and MPT in a recently published randomized trial. Their results are comparable to those seen in the IFM 9906 trial, with MPT significantly superior in CR rate and EFS. The absence of significant OS benefit is possibly caused by the short follow-up time. Although some concerns still exist about the toxicity of this regimen, MPT represents the first improvement over MP in this age group and should currently be considered standard care for elderly patients. Moreover, MPT yields CR + VGPR and survival rates that are comparable to those seen with single ASCT (Table 2).

Impressive preliminary results have also been obtained with bortezomib combined with MP.\textsuperscript{33} Therefore, some investigators already believe that ASCT could be replaced by one of these combinations, or at least that new randomized studies should again compare ASCT and conventional chemotherapy, including novel agents. However, although the arguments against ASCT involve cost and morbidity, these new combinations will be expensive and carry the risk for acute complications such as thromboembolism or chronic sequelae such as peripheral neuropathy. Moreover, results of ASCT have recently improved (Table 2). Rather than opposing ASCT and novel agents, combining them should be more useful in increasing the CR rate, prolonging the remission duration, and decreasing the need for a second ASCT.

Allogeneic SCT

Standard Allogeneic SCT
Allogeneic SCT with a conventional myeloablative preparative regimen has a limited role in multiple myeloma. Although it is probably the only curative treatment, its use is limited by toxicity. It can be proposed only to patients younger than 55 years with human leukocyte antigen-identical donor, which represents a small minority of patients. Even in younger patients, transplant-related mortality remains high because of graft-versus-host disease and infections.

A retrospective analysis of the European experience suggested that results could be improved by performing earlier transplantations,\textsuperscript{34} although 2 multicenter trials with up-front allogeneic ASCT yielded poor results.\textsuperscript{5,35} Therefore, most investigators have stopped performing standard allogeneic SCT in multiple myeloma.

Reduced-Intensity Conditioning ASCT
The so-called graft-versus-myeloma effect of the allogeneic graft has been shown with donor lymphocytes injections in patients experiencing relapse after allogeneic SCT. Nonmyeloablative or reduced-intensity conditioning regimens before allogeneic SCT represent a new hope.

The objective is to reduce transplant-related toxicity while harnessing the graft-versus-myeloma effect related to the donor immune system. Nonmyeloablative reduced-intensity conditioning is associated with a much lower transplant-related mortality and can be proposed to older patients (up to 65 years of age), even with unrelated donors.\textsuperscript{36} However, relapses are frequent when tumor burden at transplantation is high.\textsuperscript{37,38} Therefore, a strategy combining tumor-burden reduction with high-dose therapy plus ASCT and reduced-intensity conditioning allogeneic transplantation was recently developed.

Several groups have published their experience with this approach.\textsuperscript{39–41} Short-term results are encouraging, but these studies raise several concerns:

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<tr>
<th>Table 2</th>
<th>Comparison of Conventional Chemotherapy + Thalidomide with Single and Double ASCT Programs</th>
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<tbody>
<tr>
<td>MPT</td>
<td>Palumbo\textsuperscript{30} Facon\textsuperscript{31}</td>
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<tr>
<td>ASCT</td>
<td>Attal\textsuperscript{1} Child\textsuperscript{2}</td>
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<tr>
<td>Double ASCT</td>
<td>IFM 99 TTT2 Thal\textsuperscript{15}</td>
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<tr>
<td>CR (%)</td>
<td>16 15 22* 44 54.5* 62</td>
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<td>Median EFS</td>
<td>29 29.5 m 27 m 31 m 36 m 5-year 56%</td>
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<tr>
<td>Median OS</td>
<td>NR at 56 m 57 m 54 m NR at 66 m 5-year 65%</td>
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*Including VGPR
Abbreviations: ASCT, autologous stem cell transplantation; CR, complete remission; EFS, event-free survival; MPT, melphalan-prednisone and thalidomide; NR, no response; OS, overall survival; VGPR, very good partial remission.
1. Although this strategy is considerably less toxic than myeloablative allogeneic SCT, 1-year transplant-related mortality remains 10% to 15%.
2. Chronic graft-versus-host disease remains a frequent complication that causes added morbidity and mortality and can seriously impair quality of life.
3. In most studies, follow-up time is still short. With more follow-up, the relapse rate increases. Because relapse rate seems to be decreased in patients with chronic graft-versus-host disease, attempts to reduce the disease incidence and severity could increase after transplantation relapse.

With these results, and knowing the results of less dangerous approaches such as ASCT or even conventional chemotherapy combined with novel agents, proposing this tandem approach of ASCT/reduced-intensity conditioning allogeneic SCT to all patients may be difficult. The IFM group compared tandem autologous reduced-intensity conditioning allogeneic SCT and double ASCT in patients with high-risk multiple myeloma (β2-microglobulin level > 3 mg/L and del 13 using FISH analysis) and found no significant difference between the treatments. However, although transplant-related mortality was acceptable in the reduced-intensity conditioning allogeneic group, the major cause of failure was relapse.42 Relapse rate might be decreased by the use of different preparative regimens and graft-versus-host prophylaxis or by introducing novel agents after reduced-intensity conditioning allogeneic SCT.43

Clinical trials evaluating the impact of tandem autologous reduced-intensity conditioning allogeneic SCT in selected patients with multiple myeloma are still necessary.

References

13. Fermand JP. High dose therapy supported with autologous blood stem cell transplantation in multiple myeloma: long term follow-up of the prospective studies of the MAG group [abstract]. Haematologica 2005;90(suppl 1):40. Abstract PL8.05.