Autologous transplantation for multiple myeloma

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introduction

Until now high-dose therapy (HDT) supported by autologous stem cell transplantation (ASCT) has been considered the standard of care for frontline therapy of multiple myeloma (MM) in younger patients with normal renal function, and MM is currently the first indication of ASCT.

However, the introduction of the novel agents thalidomide, bortezomib and lenalidomide is changing the scenario in two ways. First, these agents can be added to HDT either before or after ASCT with the objectives of increasing the complete remission (CR) rate and of prolonging first remission duration.

Secondly, the use of novel agents as frontline therapy in combination with either dexamethasone or alkylating agents yields CR rates and progression-free survival (PFS) rates that are comparable with those achieved with HDT. Therefore, the role of ASCT is again a matter of debate: should it be used upfront or only as salvage treatment at progression in patients initially treated with novel agents?

autologous stem cell transplantation in multiple myeloma. What have we learned in the past 25 years?

ASCT versus conventional chemotherapy

The Intergroupe Francophone du Myélome (IFM) was the first to conduct a randomized trial showing the superiority of HDT with ASCT compared with conventional chemotherapy in 200 patients <65 years of age [1]. In this IFM 90 trial, HDT significantly improved the response rate, event-free survival (EFS) and overall survival (OS). Similar results were published 7 years later by the British Medical Research Council [2]. As a consequence of these two studies, ASCT became the standard of care for frontline therapy at least in younger patients (up to 65 years of age) with a normal renal function. However, other randomized studies were published in the past 10 years, and not all were that positive [3–7]. The results of seven published randomized studies are shown in Table 1.

In all but one study, the CR rate was superior in the HDT arm. In five of these seven studies this superior CR rate translated into a significant benefit in terms of PFS. It should be noticed that in the two studies which failed to show an improved PFS with ASCT, randomization was not performed at diagnosis but only after induction treatment, which may have induced a selection bias.

However, as regards OS, the superiority of ASCT was significant in only 3/7 studies. This could be explained by a better salvage treatment in the conventional chemotherapy arms.

what are the conclusions of these studies completed 10 years ago or more?

(i) The benefit of ASCT is more evident when all patients are randomized at diagnosis than when randomization is performed after induction treatment, probably because patients with resistant disease are excluded from late randomization. Patients who do not respond to initial chemotherapy should not be excluded from HDT programmes since it has been shown that ASCT is a useful salvage therapy for patients with primary refractory MM [8,9].

(ii) Compared with conventional chemotherapy, ASCT almost always increases PFS and time without symptoms or treatment toxicity, as shown in two French studies [3,6]. However, OS is not always significantly improved. A meta-analysis of 2411 patients included in randomized controlled trials comparing HDT and standard dose therapy showed a PFS benefit but no significant OS benefit for HDT [10]. This is partly explained by the impact of ASCT after relapse in patients initially treated with conventional chemotherapy. Therefore, already at that time, delayed ASCT was considered a valuable approach [3,11].

(iii) The randomized trials confirmed that ASCT significantly increased not only the response rate but also the CR rate. An important finding from the IFM 90 trial was the strong relationship between quality of response and OS [1]. Patients achieving CR or at least very good partial remission (VGPR) had longer OS than patients who had only partial remission (PR). This finding was confirmed in all subsequent IFM trials [12,13] and by other groups, at least for PFS [2,14–19]. Although the relationship between quality of response and PFS or OS is not found in all types of myeloma [20,21], a recently published meta-analysis confirmed the highly significant association between maximal response and long-term outcome [22].
Currently results of randomized trials are in favour of double ASCT. The IFM 94 trial confirmed the feasibility of double ASCT, since 75% of patients underwent the second ASCT, and the toxic death rate was <5%. However, many investigators considered the benefit of this approach to be marginal, and were concerned by cost and morbidity. Therefore, defining which patients benefited more from this aggressive management seemed important. In the IFM 94 trial, the only parameter defining patients who did not benefit from double ASCT was response to the first ASCT [12]. Patients with <90% reduction of their M-component after one ASCT had a longer OS in the double-ASCT arm, whereas patients experiencing CR or VGPR after the first ASCT had the same OS with or without the second. This finding was confirmed by the Italian group [27].

### ASCT in the era of novel agents: novel agents in combination with ASCT

**novel agents as induction treatment prior to ASCT**

The standard induction therapy in patients candidate for ASCT was dexamethasone based, either dexamethasone alone or VAD-like therapy. The primary objective of novel agents given in this context is to increase the CR rate not only prior to but also after ASCT. The increased CR rate could be converted into longer EFS and OS. Another interest would be in reducing the proportion of patients needing a second ASCT due to a less than VGPR after the first.

**Thalidomide-based regimens.** Thalidomide was the first novel agent to be used in this setting, either in combination with dexamethasone (TD), or in combination with adriamycin and dexamethasone (TAD). These combinations have been compared with dexamethasone or VAD [28–31].

In all studies, TD and TAD were both superior to dexamethasone alone or VAD in terms of response rate or VGPR rate. However, the thalidomide-based regimens did not increase the CR rate prior to ASCT, which remained very low (<10%). Post-ASCT results were analysed in two trials: while VGPR rates with TD and VAD were similar [30], the VGPR rate was superior with TAD compared with VAD [31]. Moreover, these combinations with thalidomide induced a high incidence of deep vein thrombosis (DVT). The benefit of TD compared with VAD remained modest.

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**Table 1.** Conventional chemotherapy (CC) versus high-dose therapy (HDT): results of randomized studies

<table>
<thead>
<tr>
<th>Group/trial [reference]</th>
<th>No. of patients</th>
<th>Age (years)</th>
<th>Median follow-up</th>
<th>CR rate (%) CC</th>
<th>Median EFS (months) CC</th>
<th>Median OS (months) CC</th>
<th>Median EFS (months) HDT</th>
<th>Median OS (months) HDT</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFM 90 [13]</td>
<td>200</td>
<td>&lt;65</td>
<td>7 years</td>
<td>5</td>
<td>18</td>
<td>28</td>
<td>19</td>
<td>24</td>
</tr>
<tr>
<td>MAG91 [15]</td>
<td>190</td>
<td>55–65</td>
<td>56 months</td>
<td>19</td>
<td>19</td>
<td>24</td>
<td>19</td>
<td>24</td>
</tr>
<tr>
<td>Pethema [17]</td>
<td>164</td>
<td>&lt;65</td>
<td>44 months</td>
<td>11</td>
<td>30</td>
<td>42</td>
<td>33</td>
<td>42</td>
</tr>
<tr>
<td>Italian MMMSG [16]</td>
<td>195</td>
<td>&lt;70</td>
<td>39 months</td>
<td>6</td>
<td>15.6</td>
<td>28</td>
<td>15</td>
<td>28</td>
</tr>
<tr>
<td>MRC7 [14]</td>
<td>407</td>
<td>&lt;65</td>
<td>42 months</td>
<td>8</td>
<td>44</td>
<td>31</td>
<td>9</td>
<td>31</td>
</tr>
<tr>
<td>MAG95 [18]</td>
<td>190</td>
<td>55–65</td>
<td>10 years</td>
<td>20*</td>
<td>48*</td>
<td>48</td>
<td>19</td>
<td>48</td>
</tr>
<tr>
<td>US 59321 [19]</td>
<td>516</td>
<td>≤70</td>
<td>76 months</td>
<td>15</td>
<td>17</td>
<td>14%</td>
<td>17%</td>
<td>38%</td>
</tr>
</tbody>
</table>

*ASCT, complete remission; EFS, event-free survival; OS, overall survival.*

CR, complete remission; EFS, event-free survival; OS, overall survival.

This important finding from studies on ASCT produced three consequences.

(i) CR or at least CR plus VGPR is now considered an objective of any treatment.

(ii) While the majority of randomized studies show a PFS benefit of ASCT over conventional chemotherapy, this is not the case when there is no difference in the CR rate. Indeed, in the US Intergroup trial, PFS achieved with ASCT and with conventional chemotherapy were similar [7]. This was not explained by worse results of the ASCT arm (as compared with results achieved in the IFM 90 trial for instance) but by better results in the arm with conventional chemotherapy. The CR rate obtained with chemotherapy was much better than in other trials and almost identical to that achieved with ASCT. That means that if results of chemotherapy can be improved, especially with novel agents, the difference in PFS may disappear.

(iii) Response criteria have been redefined in order to introduce the notions of CR (negative immunofixation), near-CR (nCR; negative electrophoresis but positive immunofixation) and VGPR [23,24].

**single versus double ASCT**

While attempts to improve results of ASCT by improving either the quality of the graft or the conditioning regimen were unsuccessful, another strategy based on further intensification was tested. The concept of double intensive therapy was introduced in the late 1980s with the objective of further increasing the CR rate [25]. The Arkansas group developed a double ASCT programme which yielded encouraging median EFS and OS of 43 months and 68 months, respectively, in newly diagnosed patients 26.

The IFM was again the first to conduct a randomized trial comparing single and double ASCT in 599 patients up to 60 years of age [12]. On an intent-to-treat basis, the 7-year EFS and OS were significantly improved in the double ASCT arm. The benefit in EFS but not in OS was confirmed by two other randomized studies [20,27]. Final results of two other randomized studies from France and Germany are pending. Currently results of randomized trials are in favour of double ASCT.
The addition of a third agent looks more attractive. The TCD regimen (thalidomide, cyclophosphamide, dexamethasone) is currently being tested in a large randomized study in the UK [32]. Preliminary results show high CR rates both before ASCT (20%) and after ASCT (58%).

**Bortezomib-based regimens.** Phase II studies of bortezomib plus dexamethasone (VD) regimens show very high response rates (66–88%) and an apparent increase in the CR plus VGPR rate before ASCT (22.5–31%) [33–35]. These CR plus VGPR rates are comparable with those achieved with single ASCT, and could be converted to even higher CR plus VGPR rates (55–65%) after ASCT. The most frequent adverse event with these regimens was peripheral neuropathy, which was observed in 25–30% of cases, but grade 3 was rare. However, only randomized trials could demonstrate the superiority of bortezomib-based regimens compared with classical induction treatment.

In 2005, the IFM initiated a randomized trial (IFM 2005-01) comparing four courses of induction treatment prior to ASCT with either VAD or VD [36]. Compared with VAD, the VD regimen increased not only the overall response rate (60% versus 13%; \( P < 0.0001 \)) but also the CR plus nCR rate (21% versus 8%; \( P < 0.0001 \)) and the CR plus VGPR rate (47% versus 19%; \( P < 0.0001 \)). More importantly this higher pre-ASCT efficacy translated into a higher post-ASCT CR plus nCR rate (35% versus 24%; \( P = 0.0056 \)) or CR plus VGPR rate (62% versus 42%; \( P < 0.0001 \)) on an intent-to-treat analysis.

The VD regimen was well tolerated, with no more adverse events than with the standard VAD except peripheral neuropathy (35% versus 23% but only 6% grade ≥3 with VD). Stem cell collection after priming with granulocyte colony-stimulating factor (G-CSF) alone was sufficient to allow one ASCT in 97% of patients.

Therefore, VD should now be considered a standard induction treatment prior to ASCT, with which other more complex regimens should be compared.

The addition of a third agent (doxorubicin or thalidomide) was tested in small phase II studies, and the outcome appeared even better, with response rates of ~90% and CR rates up to 24% [37–39]. Again this higher efficacy appeared to translate into very high CR plus nCR rates (>50%) after ASCT. The Italian group recently confirmed these results in a randomized trial comparing VTD and TD [40]. The CR plus nCR or CR plus VGPR rates look even better than with VD.

**Lenalidomide-based regimens.** Experience with lenalidomide in induction treatment is more limited. A small pilot study of lenalidomide plus dexamethasone (RD) in newly diagnosed patients showed an overall response rate of 91%, with 56% CR plus VGPR. In patients proceeding to ASCT, the 2-year PFS and OS were very promising (83 and 92%, respectively) [41]. Recently a randomized study comparing lenalidomide combined with either high-dose or low-dose dexamethasone showed a very high short-term OS rate with low-dose dexamethasone especially in younger patients up to 65 years of age [42]. However, in these two studies, the role of this combination as induction treatment is unclear, since only some of the patients were actually candidates for ASCT. Although the combination of lenalidomide plus dexamethasone appears to be very active, more studies in the field of ASCT are needed to evaluate the efficacy/toxicity ratio.

To summarize, induction regimens including novel agents look very promising since they increase the response rate compared with classical regimens such as VAD. Currently, VD appears superior to TD due to higher pre- and post-ASCT CR or CR plus VGPR rates. The addition of a third agent to either TD or VD could further improve results. The impact of this improved tumour reduction on PFS and OS is still unknown.

**maintenance therapy after ASCT**

Thalidomide has been tested in this setting by several groups. At least four randomized studies have been completed and are summarized in Table 2 [43–46]. Thalidomide was tested in the context of a complex protocol including induction treatment, double ASCT, consolidation therapy and interferon plus dexamethasone maintenance (Total Therapy 2) [43]. In this trial thalidomide was administered from the onset until disease progression or undue adverse effects, and 70% of patients received >2 years of treatment.

### Table 2. Randomized studies testing thalidomide as maintenance after ASCT

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>ASCT</th>
<th>Dose of thalidomide</th>
<th>Duration of treatment</th>
<th>CR rate</th>
<th>PFS</th>
<th>OS</th>
<th>PN grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barlogie (100)</td>
<td>668</td>
<td>Double</td>
<td>Start 400 mg/day</td>
<td>From the onset until relapse or toxicity</td>
<td>62% versus 43%</td>
<td>5-year PFS 56% versus 44%</td>
<td>5-year OS 65% versus 65%</td>
<td>27%</td>
</tr>
<tr>
<td>Attal (85)</td>
<td>597</td>
<td>Double</td>
<td>Median 200 mg/day</td>
<td>Until relapse or toxicity (median 15 months)</td>
<td>67% versus 55% or 57%</td>
<td>3-year PFS 52% versus 36% or 37%</td>
<td>4-year OS 87% versus 74% or 77%</td>
<td>7%</td>
</tr>
<tr>
<td>Abdelkefi (101)</td>
<td>140</td>
<td>Single</td>
<td>100 mg/day</td>
<td>6 months</td>
<td>67% versus 51%</td>
<td>3-year PFS 85% versus 57%</td>
<td>3-year OS 85% versus 65%</td>
<td>4%</td>
</tr>
<tr>
<td>Spencer (102)</td>
<td>243</td>
<td>Single</td>
<td>200 mg/day</td>
<td>12 months</td>
<td>24% versus 15%</td>
<td>2-year PFS 63% versus 36%</td>
<td>2-year OS 51% versus 80%</td>
<td>10%</td>
</tr>
</tbody>
</table>

CR, complete remission; OS, overall survival; PFS, progression-free survival.
In the IFM 9902 trial, 2 months after double ASCT, 597 patients with standard-risk MM [p<1-microglobulin ≤3 mg/l and/or no deletion 13 by fluorescence in situ homogenization (FISH)] were randomly assigned to receive no further treatment, pamidronate or thalidomide plus pamidronate [44].

The Tunisian study compared single ASCT plus thalidomide maintenance and double ASCT [45].

The Australian study compared corticosteroids alone and corticosteroids plus thalidomide [46].

(i) All studies showed a significant benefit in terms of CR (or CR + VGPR) rate and PFS, and in three of four OS was significantly prolonged as well. In the Arkansas study, OS was not improved due to a shorter survival after relapse in the thalidomide arm [43].

(ii) Except in the Arkansas study in which thalidomide was given during induction treatment in combination with dexamethasone and chemotherapy, there was no increased risk of DVT since the tumour burden is low after ASCT.

(iii) The optimum duration of thalidomide maintenance is not known. However the incidence of peripheral neuropathy observed with thalidomide is cumulative and is related to the duration of treatment. The incidence grade 3 and 4 peripheral neuropathy was 27% in the Arkansas study where treatment was prolonged, and only 4% in the Tunisian study where thalidomide was given only for 6 months. Reducing the duration of treatment could not only decrease the incidence of adverse events but could also decrease the risk of selection of resistant clones and improve the therapeutic efficacy at relapse.

(iv) In the pioneer study on thalidomide [47] as well as in the IFM 9902 study, patients with chromosome 13 deletions benefit less from this treatment. Preliminary results with bortezomib or lenalidomide suggest that these agents may overcome the poor prognosis associated with this cytogenetic abnormality [48–50]. Therefore, these agents are attractive alternatives for post-ASCT treatment that are currently being evaluated in randomized trials.

ASCT in the era of novel agents: novel agents in place of ASCT

Frontline therapy with novel agents is dramatically improving the outcome in patients who are not candidates for ASCT, especially elderly patients. Several groups have evaluated the combination of one novel agent with melphalan–prednisone (MP) [51–53].

The IFM and the Italian group have compared MP with the same combination plus thalidomide in patients older than 65 years of age [51,52]. In both studies the response rate (including the CR rate) and PFS were superior in the thalidomide arm. The OS was also longer in the thalidomide arm, although the difference was not yet significant at the time of publication in the Italian study. The logical consequence of these studies is that MP should no longer be considered the standard of care for older patients. Moreover, CR and EFS rates were comparable with those achieved in younger patients who had HDT plus ASCT.

In the large randomized VISTA trial, the MPV combination was significantly superior to MP in terms of response rate (82% versus 50%) but, most importantly, yielded an outstanding CR rate of 35% which appears to be superior to the CR rate achieved with HDT [53].

Results with lenalidomide also show high CR + VGPR rates and promising short-term PFS [41, 42].

Therefore, some investigators already state that ASCT should no longer be used in frontline therapy but that stem cells could be collected during the first months of therapy with novel agents and used only as a rescue at time of relapse or progression. However, although these results are impressive, they do not necessarily indicate the end of ASCT as primary therapy in MM for a number of reasons.

(i) In the past, the arguments against ASCT were morbidity and cost. Since the combinations using novel agents have been given for at least 9 months, they have induced toxicities (peripheral neuropathy, infections, thrombosis) and are also expensive. Quality of life is an important aspect of modern treatments. While ASCT, as a ‘single shot’ treatment, induces a severe impairment of quality of life during the short period following HDT, prolonged treatment with novel agents could also induce a delayed quality of life impairment.

(ii) More importantly, results of combinations including novel agents are often compared with results achieved in the 1990s with single ASCT. However, the results of ASCT have recently improved, especially with double ASCT and with the introduction of novel agents. For instance, in the IFM 99 trial with double stem cell transplantation, median PFS was 39 months [13]. In the thalidomide arm of Total Therapy 2, the CR rate was 62% and 5-year PFS was 56%. These results compare favourably with those achieved with MPT.

(iii) Results of ASCT could be further improved with the addition of novel agents before and after HDT. Early results of Total Therapy 3 with the addition of bortezomib to the multidrug induction DT-PACE and of VTD as consolidation and TD as maintenance after double ASCT are impressive, with 83% nCR at 2 years, and 84% 2-year EFS [54]. Moreover, results of the VISTA trial confirm that, even in the era of novel therapies, melphalan remains an important agent in the therapy of MM, and the best way to administer melphalan is at high dose with stem cell rescue.

(iv) The combination of novel agents plus ASCT could improve not only the quantity of responses but also the magnitude of response. The Italian group recently showed that consolidation with VTD after ASCT was able to induce molecular remissions in 22% of patients who were in CR or VGPR after HDT [35]. Molecular remission is a very rare event after ASCT and has been observed mostly after allogeneic SCT. Since molecular remission may be associated with long-term disease control and possibly cure, this approach opens a new avenue with ASCT.
Therefore, rather than comparing ASCT and novel agents, is should be more useful to combine ASCT with novel agents in order to increase the CR rate further, to reduce the need for a second ASCT and to prolong remission duration. Another possibility could be to compare novel agents with ASCT at the time of relapse versus frontline ASCT plus novel agents.

**conclusion**

ASCT has been the first improvement in MM therapy and has dramatically increased OS in younger patients. The introduction of three active novel agents in the past few years is going to change the frontline strategy completely, not only in older patients who could not benefit from ASCT, but also in younger patients. We already know that post-ASCT thalidomide prolongs PFS and probably OS, and that novel agents prior to ASCT increase the pre- and post-ASCT CR plus VGPR rates. Therefore, we can hope that these combinations of novel agents with ASCT will induce very high CR rates, high quality responses and prolonged PFS. However, since combinations with novel agents without ASCT induce high CR rates as well, it could be useful in the near future to design randomized studies comparing the best regimen with early ASCT with the best non-intensive regimen with ASCT at randomization. Studies should also have to address the important question of salvage treatment when several active agents have been used upfront.

**disclosures**

Speakers bureau, PharMion; Speakers bureau and advisory board, Orthobiotech/Millenium; advisory board, Celgene.

**references**