Stem Cell Transplantation in Multiple Myeloma

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Multiple myeloma (MM) is one of the key hematologic malignancies in which the impact of dose intensity has been demonstrated. Consequently, in 2005, MM was the most common disease for which autologous stem cell transplantation (ASCT) was indicated both in Europe and in the U.S. However, ASCT is not curative, and most patients relapse within a median of 3 years. Novel agents such as thalidomide (Thalidomid), bortezomib (Velcade), or lenalidomide (Revlimid) have been introduced to improve high-dose therapy, and promising results have been reported. Conversely, results from myeloablative allogeneic stem cell transplantation remain disappointing due to high transplantation-related mortality, justifying the exploration of strategies such as reduced-intensity conditioning, which have been shown to be feasible but for which proof of efficacy requires continued study.

Autologous Stem Cell Transplantation in Young Patients

Autologous stem cell transplantation versus conventional chemotherapy

The Intergroupe Francophone du Myelome (IFM) was the first to demonstrate in a randomized trial the superiority of high-dose therapy (HDT) supported by autologous bone marrow transplantation (BMT) compared with conventional chemotherapy (CC) for multiple myeloma (MM). In this IFM 90 trial, HDT significantly increased the complete remission (CR) rate, the event-free survival (EFS) and the overall survival (OS) in patients with newly diagnosed MM up to the age of 65 years.

Following this publication, similar randomized trials have been reported (Table 1). Three trials (including the IFM 90 trial) used a conditioning regimen without or with low-dose total body irradiation (TBI). HDT was found to improve OS in these three studies. High-dose TBI or high-dose busulfan was used in three other studies, and none of these studies reported a survival benefit of HDT.

The negative impact of TBI in the conditioning regimen was also shown in the IFM 95 protocol. Patients were randomized to receive high-dose melphalan (HDM) alone or HDM plus TBI supported with autologous stem cell transplantation (ASCT). The response rates and the durations of response were similar in the two groups. However, the OS was significantly improved in the HDM-alone group due to less toxicity and a better survival after relapse. In aggregate, HDM supported with ASCT should be considered as the standard of care in young patients.

Tandem autologous transplantation

In the IFM 90 trial, achievement of at least a very good partial remission (>90% reduction of the M-component) correlated significantly with longer survival. This suggests that in MM, as in other hematologic malignancies, the primary objective of induction and consolidation therapy should be to achieve CR. Barlogie and colleagues in Arkansas reported that one approach to increasing the CR rate was to repeat intensive treatments. The IFM conducted a randomized trial (IFM 94) comparing single and double ASCT. In this study, 399 previously untreated patients younger than 60 years old were randomly assigned to undergo either a single ASCT prepared by melphalan 140 mg/m² (Mel 140) plus TBI or a double ASCT, the first being prepared by Mel 140 and the second by Mel 140 plus TBI. On an intention-to-treat basis, CR or very good partial remission was achieved by 42% of patients in the single-ASCT group versus 50% in the double-ASCT group (P = .10). The probability of 7-year EFS was 10% versus 20% (P = .03), and the probability of 7-year OS was 42% versus 21%, respectively. However, the survival benefit of double transplantation was only observed among patients failing to achieve a very good partial response after the first transplantation. On the other hand, patients already in very good partial response after the first transplantation did not significantly benefit from the second one.

Table 1. Autologous stem cell transplantation versus conventional chemotherapy: randomized studies.

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Event-free survival</th>
<th>Overall survival</th>
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<tbody>
<tr>
<td>Attal et al¹</td>
<td>200</td>
<td>7-year: 16% vs 8% (P &lt; .01)</td>
<td>7-year: 43% vs 27% (P &lt; .03)</td>
</tr>
<tr>
<td>Child et al²</td>
<td>401</td>
<td>Median: 32 mo vs 20 mo (P &lt; .01)</td>
<td>Median: 54 mo vs 42 mo (P &lt; .01)</td>
</tr>
<tr>
<td>Palumbo et al³</td>
<td>194</td>
<td>3-year: 37% vs 16% (P &lt; .001)</td>
<td>3-year: 77% vs 62% (P &lt; .01)</td>
</tr>
<tr>
<td>Fermand et al⁴</td>
<td>190</td>
<td>Median: 25 mo vs 19 mo (NS)</td>
<td>Median: 47 mo vs 48 mo (NS)</td>
</tr>
<tr>
<td>Blade et al⁵</td>
<td>216</td>
<td>Median: 42 mo vs 33 mo (NS)</td>
<td>Median: 66 mo vs 61 mo (NS)</td>
</tr>
<tr>
<td>Barlogie et al⁶</td>
<td>516</td>
<td>7-year: 16% vs 17% (NS)</td>
<td>7-year: 37% vs 42% (NS)</td>
</tr>
</tbody>
</table>

Abbreviations: NS, not significant.
Similar randomized trials comparing single versus double ASCT have been reported. Three out of these 5 studies (including the IFM 94 trial) have reported a survival benefit in favor of tandem transplantation, although 2 did not. Thus, double transplantation can be proposed to young patients failing to achieve a very good response after a single transplantation as a potential treatment option, with participation in a clinical trial especially favored.

**Prognostic factors in the context of ASCT**

Despite major improvements in the survival of patients treated with HDT, a large heterogeneity is observed among the outcome of these patients. Actually, the benefit of HDT cannot be evaluated in some of them, as progression occurs prior to induction/HDT delivery. But even in those receiving the treatment, a significant variability in outcome is found. Many factors can be responsible of a lack of efficacy of HDT. Most of these factors are linked to biology, but some data raise the hypothesis that individual host genetic factors can play a role in resistance to HDT.

The recent proposal of the ISS (International Staging System) has shown that simple biological parameters, such as β2-microglobulin (β2m) and albumin levels, were able to give a quite good prediction of outcome after either conventional or high-dose chemotherapy. This system defines 3 groups of patients: stage 1 (β2m < 3.5 mg/L and albumin ≥ 35 g/L), stage 3 (β2m ≥ 5.5 mg/L), and stage 2 (other patients between stages 1 and 3). Restricted to patients treated with HDT, the OS was 111 months, 66 months, and 45 months, respectively, for patients with ISS stage 1, 2, or 3. The prognostic value of ISS in the patients treated with HDT in the IFM 99 trials has been switched and confirmed the ISS value in this series (48 months for stage 3 patients, and not reached for patients in stages 1 and 2).

However, both β2m and albumin levels reflect extrinsic factors, such as monoclonal protein characteristics, tumor mass, and/or renal insufficiency. In order to take into account intrinsic parameters of the disease itself, studies have also focused on chromosomal abnormalities. Because of the difficulties in generating metaphases within the tumor clone, most investigators used interphase fluorescence in situ hybridization (iFISH). By using this technique, several chromosomal abnormalities have been shown to have poor prognosis, including: del(13), t(4;14), del(17p), or t(14;16). In the IFM 99 trials, the prognostic impact of del(13), t(4;14), and del(17p) was studied in a large series of more than 700 patients treated with double-intensive regimens. We showed that del(13), t(4;14), and del(17p) were associated with a shorter survival. In a multivariate analysis including del(13), t(4;14), del(17p), Ig gains, β2m, anemia, thrombocytopenia, and hypoalbuminemia, we showed that 3 parameters were independent predictors of a shorter survival, specifically, t(4;14), del(17p) and high β2m. Based on these results, we have proposed a novel prognostic model: patients with low β2m (< 4 mg/L) and lacking the 2 chromosomal abnormalities (35% of the patients, with 85% alive at 4 years) enjoy a better outcome, versus patients with high β2m and 1 or 2 of the 2 cytogenetic anomalies (15% of the patients and median OS, 19 months), and other patients (50% of the patients; median OS, 4 years).

Other factors have been related with poor outcome. Among them, the more important is probably the proliferative index, with a short survival in patients presenting a high proliferation. However, this laboratory parameter is not always available or routinely evaluated. It has also been reported that the response to HDT is a prognostic factor. However, this result is typically available only after treatment and thus is of limited usefulness prior to or during initial therapy. Finally, more recent studies have reported on the use of genomics for prognostication. Analysis of patients treated in the Arkansas Total Therapy II program showed that a set of 70 (or even 17) genes could identify patients with a rapid progression. However, gene expression profiling is not considered a standard approach, and these results remain to be validated in a series of independent studies in order to become of more prognostic value.

**How to improve the outcome of ASCT: the impact of new drugs**

The introduction of novel agents such as thalidomide (THAL), bortezomib or lenalidomide in the HDT is logical and has been actively investigated to try to improve the quality of response: (1) the induction therapy, (2) HDT, and (3) maintenance therapy after ASCT.

**New drugs during the induction phase.** Patients eligible for ASCT should avoid induction therapy with alkylating agents to enable an adequate stem cell collection. Dexamethasone (DEX) alone or with vincristine and doxorubicin (the VAD regimen) has long been a standard induction regimen. However, in the last several years, different studies have reported that the association of DEX plus new drugs significantly improves the response rate before ASCT. The association of THAL and DEX has been extensively investigated. In a matched case-control analysis, Cavo et al reported 52% of partial response (PR) including 8% CR after VAD, versus 76% PR, including 10% CR after DEX-THAL (P < .001). In a phase 3 trial, Macro et al reported 7% CR after VAD, versus 25% after DEX-THAL (P < .02). In a phase 3 trial, Rajkumar et al reported 41% PR without CR after DEX, versus 63% PR, including 4% CR after DEX-THAL (P < .001). In a phase 3 trial, Goldschmidt et al reported 63% PR, including 3% of CR after VAD, versus 80% PR, including 7% CR after TAD (THAL, Adriamycin, DEX; P < .001).

The association of bortezomib and DEX has been evaluated in a pilot study of the Intergroupe Francophone du Myélome, and we found that this combination could induce a remarkable 67% PR, including 21% CR with DEX-bortezomib. This association has been compared to VAD in a large phase 3 trial (IFM 2005 01 trial). The first analysis of this protocol reported 82% PR, including 43% CR with DEX-bortezomib, versus 67% PR, including 26% CR with VAD.
The association of lenalidomide and DEX has been evaluated in a small pilot study (31 patients), and Rajkumar et al\textsuperscript{22} reported an unprecedented 91% PR, including 32% CR or near-CR.

Thus, although randomized trials are still ongoing, it is reasonable to expect these new drugs with DEX will increase the PR and CR rate before HDT as compared with VAD. Furthermore, since an adequate stem cell collection has been obtained with these newer induction regimens, and in particular with bortezomib, VAD should no longer be considered as the standard induction regimen.

\textit{New drugs combined with the high-dose regimen.} In MM, the standard HDT is single-agent Mel at a dosage of 200 mg/m\textsuperscript{2}. Attempts to improve this regimen with conventional drugs or TBI have failed to improve the response rate but have increased both hematologic and nonhematologic toxicities. A synergistic effect between bortezomib and Mel has been demonstrated \textit{in vitro} and \textit{in vivo}. Furthermore, the toxicity of these two drugs is different. Thus, the combination of bortezomib and HDM is a logical approach to study, and we have conducted a pilot trial of HDM (200 mg/m\textsuperscript{2} on day –2) and bortezomib (1 mg/m\textsuperscript{2} on days –6, –3, +1, +4) supported with ASCT (day 0). Thirty-five patients with poor-risk features (defined as failing to achieve PR after induction therapy \([n = 26]\) or failing to achieve a very good partial response [VGPR] after a first transplant \([n = 9]\)) were enrolled. No toxic death occurred, and the median durations of neutropenia (<500/mm\textsuperscript{3}) and thrombocytopenia (<20,000/mm\textsuperscript{3}) were 7 and 1 day, respectively. The incidence of severe mucositis (grade 3/4) was manageable at 20%. Three months after ASCT, a dramatic ORR of 63% VGPR, including 31% of true CR, was observed. Furthermore, 6 of 9 patients failing to achieve VGPR after the first ASCT prepared with Mel alone achieved CR (\(n = 4\)) or VGPR (\(n = 2\)) with this combination. Thus, this study suggests that the combination of bortezomib and Mel could substantially improve the VGPR rate compared with Mel alone without additive toxicity. Since the achievement of VGPR has been shown to be one of the most important prognostic factors for survival after HDT, this combination could improve the OS.

\textit{New drugs as consolidation/maintenance therapy after transplantation.} The role of maintenance therapy in MM remains an area of active investigation. Maintenance chemotherapy has failed to demonstrate any benefit. Most randomized studies and meta-analyses evaluating maintenance interferon showed a modest increase in progression-free survival (PFS) with minimal or no survival benefit after conventional therapy or HDT, and added toxicity. Corticosteroid maintenance was found to prolong the duration of response; however, the impact on survival has been modest.\textsuperscript{23,24} THAL is an oral agent with immunomodulatory properties, which is active in one-third of patients with refractory disease at doses as low as 50 mg and without myelosuppressive toxicity. Thus, THAL was an attractive candidate for use in maintenance situations, particularly after HDT. In 1999, the IFM initiated a randomized trial (IFM 99 02) designed to evaluate the role of THAL as maintenance treatment after transplantation.\textsuperscript{25} Two months after ASCT, 597 patients under the age of 65 years were randomly assigned to receive no maintenance (arm A), pamidronate (arm B), or pamidronate plus THAL (arm C). THAL was administered for a median duration of 15 months, at a mean dosage of 200 mg per day. CR or VGPR was achieved by 55% of patients in arm A, 57% in arm B, and 67% in arm C \((P = .03)\). The 3-year post-randomization probability of EFS was 36% in arm A, 37% in arm B, and 52% in arm C \((P < .009)\). The 4-year post-diagnosis probability of OS was 77% in arm A, 74% in arm B, and 87% in arm C \((P < .04)\) respectively. The proportion of patients who had skeletal events requiring a specific therapy (chemotherapy, irradiation or surgery) was 24% in arm A, 21% in arm B, and 18% in arm C \((P = .4)\). Thus, THAL improves response rate, EFS and OS in patients with myeloma and should be recommended. However, the survival benefit of THAL was not observed among patients already in VGPR after ASCT, suggesting that this benefit was not related to a maintenance effect. The survival benefit of THAL was only observed among patients failing to achieve a VGPR after ASCT, suggesting that this benefit was due to reduction of residual tumor mass. Since THAL improves survival by a consolidation effect rather than by a pure maintenance effect, stopping THAL as soon as a VGPR has been reached (2 or 3 months) could be an effective strategy to consider in order to reduce the side effects and to avoid drug resistance at time of relapse. Furthermore, 39% of patients had to discontinue THAL due to drug-related adverse events and peripheral neuropathy was the main reason for discontinuation. Thus, lenalidomide, a more potent analog of THAL without neurologic toxicities, might be an attractive candidate for use in consolidation and maintenance situations after ASCT. Consolidation/maintenance treatment with lenalidomide is currently being evaluated by several different groups (IFM, Southwest Oncology Group [SWOG], and Cancer and Leukemia Group B [CALGB]) in Europe and the U.S.

\textbf{Conclusions in young patients}

In young patients, the impact of dose intensity has been demonstrated, and single HDT supported with ASCT using a conditioning regimen with Mel alone (without TBI) should be considered a standard of care. Double transplantation can be proposed to patients failing to achieve a VGPR after a first ASCT, ideally as part of a clinical trial. Furthermore, the introduction of new drugs in the high-dose strategy (induction, HDT, consolidation and maintenance) appears to dramatically improve CR (up to 70% to 80% can be expected) and response duration. Conversely, different studies have reported that the combination of CC plus new drugs can induce 70% to 90% PR and 30% to 40% CR. Thus, new prospective trials are required to compare new drugs plus conventional chemotherapy versus new drugs plus HDT/ASCT.
Autologous Stem Cell Transplantation in Elderly Patients

In elderly patients, the situation of HDT is different. The impact of dose intensity on survival has never been demonstrated. In the IFM 90 protocol,\textsuperscript{1} the OS of patients aged older than 60 years was similar in the CC arm and in the HDT arm. In the IFM 99 06 protocol,\textsuperscript{26} 336 patients older than 65 years were randomized to receive melphalan/prednisone (MP), or MP plus THAL (MPT), or HDT (double HDT prepared with HDM at 100 mg/m\textsuperscript{2}). HDT was found to significantly improve the response rate as compared with MP (41% versus 7% VGPR). However, a similar EFS (median, 17 months with MP versus 19 months with HDT) and a similar OS (median, 30 months with MP versus 38 months with HDT) was observed between the two treatment groups. Conversely, MPT was found to significantly improve response rate (49% VGPR), EFS (median, 30 months) and OS (median not reached at 56 months) as compared with both MP and HDT. Thus, in elderly patients, HDT does not improve the OS as compared with CC and should not be recommended, but the combination of new drugs with CC can be considered the standard of care.

**Allogeneic Stem Cell Transplantation**

**Allogeneic stem cell transplantation after myeloablative conditioning regimen**

Allogeneic stem cell transplantation (SCT) was introduced in the treatment of MM 25 years ago. However, toxicity was excessively high, with a transplant-related mortality (TRM) in excess of 50% in studies including heavily pretreated patients\textsuperscript{27}. As a consequence of this prohibitive toxicity, allogeneic SCT could not be proposed to patients older than 50 to 55 years while the median age at diagnosis for patients with MM is 65, and only a small minority of younger patients had an HLA-identical sibling and could be considered eligible for this approach.

However, an improvement in outcome was observed when allogeneic SCT was proposed earlier in the course of the disease and a retrospective survey of the European Bone Marrow Transplantation (EBMT) registry showed that survival was significantly better in patients who underwent transplantation between 1994 and 1998, compared to patients who underwent transplantation prior to 1994.\textsuperscript{28} This result was due to a lower toxic death rate and a better patient selection (specifically, earlier transplantation in less heavily pretreated patients). Nonetheless, even in newly diagnosed patients, toxicity was too high, specifically in the randomized U.S. Intergroup trial comparing HDT and CC, patients up to the age of 55, and having a matched sibling were offered an allogeneic SCT with myeloablative conditioning. This treatment arm was closed after 36 patients were treated and a TRM rate of 53%.\textsuperscript{6} One way to decrease TRM is T-cell depletion, since many toxic deaths were related to the high rates of graft-versus-host disease (GVHD). Encouraging short-term results have been obtained in single-center studies with CD6 T-cell-depleted allogeneic SCT followed by prophylactic CD4+ donor lymphocyte infusions to reduce the risk of relapse.\textsuperscript{29} Unfortunately, a Dutch randomized, phase 3 prospective study using variable levels of T-cell depletion showed very poor results, with both a high toxic death rate and a high relapse rate.\textsuperscript{30}

Therefore, full-dose allogeneic SCT with a myeloablative conditioning regimen is considered excessively toxic for most patients and could only be considered as part of a clinical trial using novel strategies to both reduce toxicity and enhance efficacy.

**Reduced-intensity conditioning regimens**

Long-term follow-up of patients treated with myeloablative allogeneic SCT has shown a plateau of EFS and OS curves after 4 to 5 years in the minority of patients who survive the early post-transplantation period. This plateau has been attributed to the immunological effect of donor lymphoid cells, the so-called graft-versus-myeloma (GVM) effect. Proof of this GVM effect was supported by remissions obtained by following donor lymphocyte infusions (DLI) in patients relapsing after allogeneic BMT. This antitumor effect of donor immunocompetent cells is the basis of the introduction of reduced-intensity conditioning (RIC) allogeneic SCT in MM, in which the underlying principle is to reduce transplantation-related toxicity while harnessing the GVM effect. As a result of the retrospective analysis of 229 patients who received a RIC allograft for MM in 33 centers within the EBMT group, several important prognostic factors can be defined.\textsuperscript{31} In this series, the median age was 52 years, 14% of patients were older than 60 years, and the donor was unrelated in 16% of patients. One-year TRM was 22%, and 3-year PFS and OS were 21% and 41%, respectively. The 3-year PFS and OS were significantly better when RIC allotransplantation was performed in first remission (34% and 67%, respectively). On multivariate analysis, a decreased OS was associated with chemoresistant disease and more than 1 prior autologous transplantation. Chronic GVHD (cGVHD) was associated with better OS and PFS (84% and 46% for limited cGVHD, respectively, versus 29% and 12% in the absence of cGVHD). Therefore, this large survey suggests that RIC is feasible and yields encouraging results in first remission, but concludes that heavily pretreated patients and patients with progressive disease do not appear to benefit from this strategy. The EBMT more recently published a comparison between 320 RIC and 196 myeloablative allografts performed between 1998 and 2002 in 103 centers.\textsuperscript{32} There were significant differences between the two groups, since RIC patients were older (median age, 51 vs 45 years), more often had progressive disease (28% vs 21%), and were more likely to have received one prior ASCT (76% vs 11%). This retrospective comparison confirmed that TRM was decreased with RIC allogeneic SCT (24% vs 37% at 2 years). However, the
reduction in TRM was offset by an increase in the relapse risk for the RIC approach. As a consequence, the 3-year PFS was 19% with RIC and 35% with myeloablative alloSCT; remarkably, the 3-year OS was 38% versus 51%, respectively. Interestingly, the use of T-cell depletion, especially the use of alemtuzumab, was associated with a higher relapse risk after RIC alloSCT.

Collectively, these results suggest that RIC alloSCT should not be offered to patients with advanced MM, as the allogeneic GVM effect is not likely sufficient to induce a stable control of the disease. Furthermore, in the RIC allogeneic SCT, conditioning and GVHD prophylaxis should be carefully chosen to enhance GVM effect and minimize risk of GVHD with use of matched sibling donors strongly favored and participation in clinical trials required.

**Tandem auto-RIC allogeneic SCT**

Currently, RIC alloSCT is increasingly used after tumor reduction with HDT followed by ASCT. The feasibility of RIC alloSCT after 1 or even 2 ASCTs has been shown by the Arkansas group.8 Two groups have also reported their preliminary results with a planned tandem autologous/RIC alloSCT approach.9,10 In both studies, the CR rate achieved after RIC alloSCT was greater than 50% and the early mortality rate less than 10%. These results were considered sufficiently encouraging to justify prospective trials comparing this tandem ASCT/RIC allo approach with double ASCT.

To date, only two trials of this approach have been published,11 12 although several others in the U.S. and Europe are ongoing. The design of the two published studies was similar but had important differences. While in the Italian study all patients with an HLA-identical sibling were candidates for this approach only if they had two adverse prognostic factors (high β2m level and chromosome 13 deletion by FISH analysis). Moreover, in the Italian study, the conditioning regimen was based on low-dose TBI, while in the IFM study, it was based on fludarabine and antithymocyte globulin. Although the TRM was low in both studies (10% and 11%, respectively), the overall results were markedly different. In the IFM study, the outcome of high-risk patients was not improved by the use of RIC alloSCT; while the EFS was similar (median EFS, 18 months vs 22 months), the OS was significantly longer in the double ASCT group due to a significantly longer survival after relapse (35 months vs 59 months). In the Italian study, the CR rate was higher in the tandem auto/RIC allo group (55% vs 26%). As a consequence, at a median follow-up of 66 months, the median EFS were 43 and 33 months, respectively (P = .07), and the median OS had not been reached in the auto-RIC alloSCT group, while it was 58 months in the double-ASCT group (P = .03) at the time of publication. This superiority was apparently due to a lower rate of disease-related mortality (7% vs 43%; P < .001) between the arms, while the TRM was not significantly different. There are some methodologic concerns in the Italian study, since the number of patients with an HLA-identical sibling was almost identical to the number of patients without, which is highly unusual. Moreover, the results of double ASCT are remarkably poor and certainly inferior to those achieved currently in other studies of unselected of patients with newly diagnosed MM. Conversely, in the IFM program, the post-alloSCT relapse rate was high (57%), which could be explained by the high doses of antithymocyte globulin used in the conditioning regimen, and so this potent pretransplantation immune suppression might have prevented a GVM effect and explain the lower rate of TRM. Nonetheless, in aggregate, these results achieved with tandem auto-RIC/alloSCT are sufficiently encouraging to justify further evaluation as part of prospective clinical trials and results of other ongoing studies are awaited with interest.

In conclusion, the major question regarding the use of auto-RIC/alloSCT procedure in patients with newly diagnosed MM is currently unsolved: should it be proposed to all patients with an HLA identical donor, or should it be proposed to selected patients? It is not clear whether this strategy could improve the outcome of patients who have a poor prognosis with ASCT or with conventional chemotherapy. In the German experience, patients with 13q deletion (n = 31) had a lower 2-year EFS rate (18% vs 42%) and a lower 2-year OS rate (18% vs 47%) than patients without this abnormality.13 This finding was confirmed by the IFM trial, which showed no benefit to the tandem auto/RIC alloSCT approach compared with a double-ASCT program in such patients.11 In the Italian study, neither a high β2m level nor the presence of chromosome 13 abnormalities appeared to affect the outcome after RIC alloSCT. In patients with standard-risk MM, maintenance therapy with THAL after a double-ASCT program yielded prolonged OS (5-year OS: 85%). Thus, in this cohort of patients, the toxicity induced by RIC alloSCT (TRM, 10%-15%; cGVHD 35%-50%) is probably not justified, and as emphasised above, RIC alloSCT for newly diagnosed myeloma should remain limited to clinical trials.

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