

## REVIEW

# The allogeneic dilemma

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**The place of allogeneic SCT in the management of multiple myeloma remains controversial. Although it may induce long-term clinical and molecular remissions, the very high transplant-related toxicity after a myeloablative preparative regimen has limited its role to younger patients as first-line treatment option. Even with this limited indication, toxic death rate related to infections and GVHD is considered too high and this strategy has been almost abandoned. Reduced intensity conditioning (RIC) regimens look promising, as the transplant-related mortality is low even with matched unrelated donors and can be considered for older patients up to the age of 65 years. However when used in patients with a high tumor burden or with chemo-resistant disease, the immunologic effect of the graft is not sufficient to avoid relapses. Therefore, RIC allotransplantation is currently used after tumor mass reduction with high-dose therapy followed by autologous SCT. A recently published Italian study shows that this strategy induces better event-free survival than double autologous SCT due to a reduced relapse rate. The questions raised by this encouraging result are discussed in this paper.**

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### Introduction

Allogeneic SCT was introduced in the treatment of multiple myeloma (MM) 25 years ago, yet its role remains controversial.

Although allogeneic SCT is possibly the only curative treatment and can induce molecular remissions and long-term clinical CR, only a minority of younger patients having an HLA-identical sibling are eligible to receive this. Moreover, toxicity related to infections and to GVHD is very high, even in newly diagnosed patients, hence this strategy has almost been abandoned in recent years.

The introduction of reduced-intensity conditioning (RIC) is changing the scenario. In view of reduced transplant-related mortality (TRM), older patients (up to the age of 65 years) may be eligible for this. However, the beneficial effect of lower toxicity may be mitigated by a higher relapse rate and clinical trials are still needed to evaluate the impact of this strategy.

### Myeloablative regimens

Soon after the publication of initial clinical studies, the paradox became evident. If given early in the course of the disease, allogeneic SCT could induce molecular remissions<sup>1</sup> and approximately one-third of the patients remained free of disease 6 years later.<sup>2</sup> Therefore allogeneic SCT appeared to be the only available therapy with a potential for cure or long-term disease control in at least some patients. However, toxicity was excessively high with a TRM up to 50% in some studies including a high percentage of previously treated patients.<sup>2–4</sup> Mortality was mostly related to infections and to GVHD-related complications. As a consequence of this toxicity, allogeneic SCT could not be proposed to patients older than 50–55 years, while the median age at diagnosis was over 65 years and only a small minority of younger patients with an HLA-identical sibling could be eligible for this approach. Moreover, since toxic deaths occurred mostly during the first year, short-term comparisons of allogeneic SCT and autologous SCT were in favour of autologous SCT.<sup>5,6</sup>

An improvement of outcome was observed when allogeneic SCT was proposed at earlier stages. A retrospective survey of the EBMT registry showed that survival was significantly better in patients transplanted between 1994 and 1998, compared with patients transplanted before 1994.<sup>7</sup> This result was due to a lower toxic death rate but was not explained by a change in the source of hematopoietic stem cells (peripheral blood vs marrow) or by the use of T-cell depletion. The only explanation for a reduced TRM was a better selection of patients, with earlier transplantations in less heavily pre-treated patients. However, even in newly diagnosed patients, toxicity was considered too high. In the US Intergroup trial, comparing autologous SCT and conventional chemotherapy, patients up to the age of 55 years and having a matched sibling were offered an allogeneic SCT with myeloablative conditioning. This arm was prematurely closed after 36 patients were treated, due to a TRM rate of 53%.<sup>8</sup>

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Another way to decrease TRM could have been T-cell depletion since many toxic deaths were related to GVHD. Encouraging short-term results have been seen with CD6 T-cell-depleted allogeneic SCT followed by prophylactic CD4+ donor lymphocyte infusions to reduce the risk of relapse.<sup>9</sup> Unfortunately, a Dutch prospective study using variable levels of T-cell depletion showed poor results with both a high TRM and a high early relapse rate.<sup>10</sup>

Therefore, allogeneic SCT after myeloablative conditioning regimen was considered too risky by majority of investigators and is currently almost abandoned.

### RIC regimens

However, there was at least one argument in favor of pursuing allogeneic SCT in MM, which was the possibility of achieving long-term remissions. While with autologous SCT the risk of relapse continues, with allogeneic SCT there is a plateau of event-free survival (EFS) and overall survival (OS) curves after 4–5 years.<sup>8,11</sup> In the US Intergroup trial, the 7-year EFS was 22% for patients receiving allogeneic SCT with no further event at 10 years, suggesting that these patients could be cured.<sup>8</sup> Therefore, long-term survival could be superior with allogeneic SCT compared with autologous SCT. Much of the clinical impact of allogeneic SCT has been attributed to the immunological effect of donor lymphoid cells, which is called graft-versus-tumor effect. This effect is often associated with GVHD. While attempts to reduce GVHD have frequently been associated with a higher incidence of relapse, small retrospective studies were in favor of a graft-versus-myeloma effect associated with GVHD.<sup>12,13</sup> Proof of the graft-versus-myeloma effect was obtained by the occurrence of remissions following donor lymphocyte infusions in patients relapsing after allogeneic SCT.<sup>14–16</sup>

Again, the likelihood of a graft-versus-myeloma effect was higher in patients with GVHD.<sup>17,18</sup> This antitumor effect of donor immunocompetent cells is the basis of the introduction of RIC allogeneic SCT in a variety of hematological malignancies including MM. The principle of RIC allogeneic SCT is to reduce TRM while harnessing graft-versus-myeloma effect. Therefore, RIC allogeneic SCT represented a new hope in MM. A number of pilot studies have been performed<sup>19–24</sup> and are summarized in Table 1. Conditioning regimens were heterogeneous but always contained fludarabine often combined with low-dose TBI or with alkylating agents (melphalan, cyclophosphamide or busulfan). Antithymocyte globulin or alemtuzumab were sometimes added with the objectives of improving engraftment and reducing GVHD. GVHD prophylaxis included cyclosporine (or Tacrolimus) combined with mycophenolate mofetil or methotrexate. These studies confirm the feasibility of RIC allogeneic SCT in MM. When the information was available, full chimerism was obtained in virtually all patients. Overall TRM ranged from 15 to 20%. The rate of GVHD (grades II–IV) was between 25 and 46% and GVHD occurred in 27–70% patients. The CR rate varied from 10 to 35% and short-term OS (usually 2-year) ranged from 30 to 71%.

This preliminary experience also confirmed that RIC allogeneic SCT was possible in older patients (over 60 years of age) and with matched-unrelated donors.<sup>20,22,25</sup> However, it was soon apparent that relapses were frequent when RIC allogeneic SCT were used in relapsed/refractory patients.<sup>19,20</sup> The overall outcome (CR rate, progression free survival (PFS) and OS) was related to the status of the disease at the time of transplantation. A retrospective analysis of 229 patients who received a RIC allograft for MM in 33 centers within the EBMT group helps to define prognostic factors.<sup>26</sup> In this multicentre experience, the median age was 52 years and 14% of patients were

**Table 1** Reduced-intensity conditioning allogeneic transplantation in multiple myeloma

Reference	Number of patients (unrelated donors)	Conditioning regimen	GVHD prophylaxis	Acute GVHD (%) (grades II–IV)	Chronic GVHD (%)	TRM (%)	CR (%)	OS (%) (at-year)
Giralt <sup>19</sup>	22 (9)	Flu Mel	Tacro MTX	46	27	41	32	30 (2)
Einsle <sup>20</sup>	22 (15)	TBI Flu C	CSA MMF	38	32	20	35	58 (2)
Peggs <sup>21</sup>	20 (8)	TBI Flu Campath	CSA MMF CSA	25	—	15	10 <sup>a</sup>	71 (2)
Perez-Simon <sup>22</sup>	29	Flu Mel	MTX CSA	41	51	21	28 <sup>b</sup>	60 (2)
Mohty <sup>23</sup>	41 (0)	Bu Flu ATG	MTX CSA	36	41	17	27	62 (2)
Gerull <sup>24</sup>	52 (20)	TBI Flu	MMF	37	70	17	27	4 (1.5)

Abbreviations: ATG = antithymocyte globulin; Bu Flu = busulfan fludarabine; CSA = cyclosporine; Flu = fludarabine; Flu C = fludarabine cyclophosphamide; Mel = melphalan; MMF = mycophenolate mofetil; Tacro = tacrolimus; TRM = transplant-related mortality.

<sup>a</sup>Fourteen received DLI for residual/progressive disease.

<sup>b</sup>37% with acute GVHD vs 13% without.

older than 60 years. Fludarabine was used in 95% of patients and frequently combined to an antibody (antithymocyte globulin 79 and alemtuzumab 55). The source of stem cells was mostly peripheral blood (183/229) and the donor was unrelated in 16% of cases. One-year TRM was 22%, 3-year PFS and OS were 21 and 41%, respectively. The outcome was affected neither by the type of conditioning regimen nor by GVHD prophylaxis, but PFS was decreased in patients receiving alemtuzumab. While 3-year PFS and OS were significantly better when RIC allogeneic SCT was performed in first remission (34 and 67%, respectively), in multivariate analysis, decreased OS was associated with chemoresistant disease and with more than one prior autologous SCT. The rate of acute GVHD (grades II–IV) was 31%. Chronic GVHD (cGVHD) was associated with better OS and PFS (84 and 46%, respectively for limited cGVHD vs 29 and 12% in the absence of cGVHD). This finding confirms preliminary results on smaller series and is again in favor of graft-versus-myeloma effect.<sup>22,23,27,28</sup> Therefore, this large survey confirms that RIC allogeneic SCT is feasible even in patients older than 60 years, yields encouraging results in first remission, but that heavily pre-treated patients and patients with progressive disease do not benefit. In another retrospective analysis on 120 patients, relapse to a prior autograft was also an important adverse prognostic factor, while cGVHD reduced relapse rate.<sup>20</sup> Interestingly, in patients with chemosensitive disease and without relapse after prior autograft, 1-year TRM was only 8%.

The EBMT group recently published a comparison between 320 RIC and 196 myeloablative allogeneic SCT performed between 1998 and 2002 in 103 centres.<sup>29</sup> There were significant differences between the two groups since RIC patients were older (median age 51 vs 45 years), have more often progressive disease (28 vs 21%) and had more frequently received one prior autologous SCT (76 vs 11%). RIC allogeneic SCT done later included more T-cell depletion. Despite the use of multivariate models to take into account these differences, it is difficult to draw definite conclusions from this study but randomized studies which would allow a more convincing comparison between myeloablative and RIC allogeneic SCT are not available and will probably not be performed in the near future. Therefore, this retrospective comparison confirmed that TRM was decreased with RIC allogeneic SCT (at 2 years 24 vs 37%,  $P=0.002$ ). However the reduction in TRM was offset by an increase in the relapse risk (hazards ratio (HR)=1.9). As a consequence, the 3-year PFS was 19% with RIC and 34.5% with myeloablative allogeneic SCT ( $P=0.001$ ), the 3-year OS was 38 vs 51%. Again the use of T-cell depletion and specially the use of alemtuzumab was associated with a higher relapse risk after RIC. Collectively, these results suggest that RIC allogeneic SCT should not be offered to patients with advanced MM. The allogeneic graft-versus-myeloma effect is not sufficient though there remains some benefit from high-dose therapy to reduce tumor burden. Furthermore, in the RIC allogeneic SCT, the modalities of conditioning and GVHD prophylaxis should be carefully chosen to enhance graft-versus-myeloma effect.

## Tandem auto/RIC allotransplants

Currently, RIC allogeneic SCT is mostly used after tumor burden reduction with high-dose therapy followed by autologous SCT. The feasibility of RIC allogeneic SCT after one or even two autologous SCT has been shown by the Arkansas group.<sup>30</sup> Two groups reported their preliminary results with a planned tandem autologous followed by RIC allogeneic SCT approach.<sup>31,32</sup> Before autologous SCT, they used high-dose melphalan (200 mg/m<sup>2</sup>), which yields a high response rate with a low TRM. Before RIC allogeneic SCT, the Seattle group used low-dose TBI (200 cGy), which had been associated with a high rate of engraftment in the canine model. The German group used an immunosuppressive regimen combining fludarabine, antithymocyte globulin and melphalan. In both studies, the CR rate after RIC allogeneic SCT was more than 50% and the early TRM less than 10%. The results of these two studies are shown in Table 2. At the time of publication, follow-up time was still short and relapses occurred later. For instance, while 2-year PFS was 55% in the Seattle paper with a median follow-up time less than 2 years, relapses occurred in the third year, leading to a 4-year PFS of only 40% (Bensinger, personal communication). Nevertheless, these results were considered encouraging enough to justify prospective trials comparing this tandem auto/RIC allogeneic SCT approach with double autologous SCT, which had been previously shown superior to single autologous SCT.<sup>33</sup>

Large prospective trials have been performed in the United States and in Europe, but all the results are not available. Until now, only two trials have been published.<sup>34,35</sup> The approach of these two studies were different. While in the Italian study, all patients with an HLA-identical sibling were to proceed to RIC allogeneic SCT after autologous SCT, in the French study, patients were candidates to this approach only if they had two adverse prognostic factors (high  $\beta$ 2-microglobulin level and chromosome 13 deletion by FISH analysis). Moreover, in the Italian study, the conditioning regimen was based on low-dose TBI, whereas in the French IFM study, it was based on fludarabine and antithymocyte globulin. While in the two studies, the TRM was low (10 and 11%), the overall results are different. In the IFM study, the outcome of high-risk patients was not improved by the use of RIC allogeneic SCT.<sup>34</sup> In the updated analysis, with a median follow-up of 38 months, EFS was similar in the RIC allogeneic SCT and the double autologous SCT group both on intention-to-treat basis (median EFS 18 vs 22 months, respectively) and in patients who actually received the planned treatment (median EFS 21 vs 25 months, respectively).<sup>36</sup> Moreover, OS was significantly longer in the double autologous SCT group due to a longer survival after relapse (35 vs 59 months,  $P=0.016$ ). In the Italian study, the CR rate was significantly higher in the tandem auto/RIC allogeneic SCT group (55 vs 26%). As a consequence, at a median follow-up of 66 months, the median EFS were 43 and 33 months ( $P=0.07$ ), respectively, and the median OS has not been reached in the auto/RIC allogeneic SCT group, while it is 58 months in the double autologous SCT group ( $P=0.03$ ). This superiority

**Table 2** Tandem auto/RIC allogeneic SCT: preliminary experiences

References	Number of patients	Median age (range)	Autologous SCT conditioning regimen	Allogeneic SCT		Results						
				Conditioning regimen	GVHD prophylaxis	Chimerism	TRM	CR (%)	Acute GVHD $\geq 2$ (%)	Chronic GVHD (%)	PFS (%)	OS (%)
Kroger <sup>31</sup>	17	51 (32–66)	Mel 200	Flu Mel ATG	CSA MTX	100%	10% at 100 days 26% at 1 year	73	38	40	56	74
Maloney <sup>32</sup>	54	52 (29–71)	Mel 200	Two G $\pm$ F (n=9)	CSA MMF	100%	0% at 100 days 15% at 1 year	57	38	46	55	78

Abbreviations: ATG = antithymocyte globulin; Flu = fludarabine; G = grays; Mel = melphalan; MMF = mycophenolate mofetil.

is due to a lower rate of disease-related mortality (7 vs 43%,  $P < 0.001$ ), while the TRM was not significantly different. There are some methodological concerns in the Italian study since the number of patients with an HLA-identical sibling ( $n = 80$ ) was almost identical to the number of patients without ( $n = 84$ ). Moreover, the results of double autologous SCT are not optimal and certainly inferior to those achieved currently in an unselected population of patients with newly diagnosed MM. However, these results achieved with tandem auto/RIC allogeneic SCT are indeed very encouraging and justify further clinical evaluation. Contrary to this, in the IFM program, the post allogeneic SCT relapse rate was high (56.5%, 26/46 patients), which could be explained by the high dose of antithymocyte globulin used in the conditioning regimen. This potent pre-transplantation immune suppression might have prevented graft-versus-myeloma effects.

### Current questions to be addressed

*Should all patients with an HLA-identical donor be offered a tandem auto/RIC allogeneic SCT procedure?*

Apparently, patients who have a poor prognosis with autologous SCT or with conventional chemotherapy do not have a better outcome with this strategy. For instance, 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.<sup>37</sup> This finding was confirmed by the IFM trial showing no benefit of the tandem auto/RIC allogeneic SCT approach compared to a double autologous SCT program.<sup>34</sup> On the other hand, in the Italian study, neither a high  $\beta_2$ -microglobulin level nor presence of chromosome 13 abnormalities appeared to affect the outcome after allogeneic SCT. Therefore, in this subgroup of patients, this approach should be offered only in the context of a clinical trial.

In patients with standard-risk MM, there is currently no available comparison of the RIC allogeneic SCT approach v autologous SCT or even nonintensive therapy including novel agents (thalidomide, lenalidomide or bortezomib). In this subgroup of patients, maintenance therapy with thalidomide after a double autologous SCT program yielded prolonged EFS and OS compared to no further

treatment (or only pamidronate long-term treatment): the 3-year EFS was 52% (calculated after autologous SCT) and the 4-year OS was 87%.<sup>38</sup> Results of two large prospective studies in Europe and in North America will clarify the role of tandem auto/RIC allogeneic SCT in standard risk patients. The arguments in favor of tandem auto/RIC allogeneic SCT could be even less in good-risk patients. Even though TRM is reduced with RIC allogeneic SCT, compared to standard myeloablative regimens, it remains in the order of 10–15% for newly diagnosed patients and the risk of cGVHD is still 35–50%. Considering that the very good results achieved with single or tandem autologous SCT in patients with no adverse prognostic factor<sup>39,40</sup> could be further improved by the introduction of novel therapies, these risks of toxicity are probably not justified in this cohort of patients.

*Could results RIC allogeneic SCT be further improved?*

Although, the results of the Italian study are very encouraging, only 21 of the 58 patients who completed the auto/RIC allogeneic SCT program were still in CR after a median follow-up of 38 months. Since the TRM has been reduced, the objective should now be to increase the CR rate and reduce the relapse rate. The use of donor lymphocyte infusions did not appear to increase the CR rate in the Italian study (only four treated partial remissions in 11 patients).<sup>35</sup> They should be used early after allogeneic SCT (persistent disease without acute GVHD). When used for confirmed disease relapse, the chance of achieving a response is probably very low.

Another possibility to improve efficacy could be to use the novel agents after RIC allogeneic SCT. Remissions have been achieved with thalidomide or bortezomib in patients with residual or progressive disease after RIC allogeneic SCT.<sup>41–44</sup> Therefore, these agents could also be used to maintain remission after RIC allogeneic SCT.<sup>45</sup>

### Conclusions

- (1) Despite the possibility of achieving some long-term remissions, myeloablative regimens before allogeneic SCT should not be used routinely. This approach

should be considered within the setting of a clinical trial (for instance, testing new conditioning regimens).

- (2) RIC allogeneic SCT should be considered for patients with chemosensitive disease and with a low tumor burden, which can be obtained after high-dose therapy plus autologous SCT.
- (3) Results of RIC allogeneic SCT should not be published too early because of the risk of delayed relapses.
- (4) Results of tandem auto/RIC allogeneic SCT in newly diagnosed patients are encouraging, but should be evaluated in relation with initial prognostic factors.
- (5) Part of the graft-versus-myeloma effect remains related to cGVHD that can induce mortality and morbidity.

Results of ongoing trials will determine the place of tandem auto/RIC allogeneic SCT, in the context of the new treatment paradigm related to the introduction of novel agents like thalidomide, bortezomib and lenalidomide.

## References

- 1 Corradini P, Voena C, Tarella C, Astolfi M, Ladetto M, Palumbo A *et al.* Molecular and clinical remissions in multiple myeloma: role of autologous and allogeneic transplantation of hematopoietic cells. *J Clin Oncol* 1999; **17**: 208–215.
- 2 Gahrton G, Tura S, Ljungman P, Blade J, Brandt L, Cavo M *et al.* Prognostic factors in allogeneic bone marrow transplantation for multiple myeloma. *J Clin Oncol* 1995; **13**: 1312–1322.
- 3 Bensinger WI, Buckner CD, Anasetti C, Clift R, Storb R, Barnett T *et al.* Allogeneic marrow transplantation for multiple myeloma: an analysis of risk factors on outcome. *Blood* 1996; **88**: 2787–2793.
- 4 Mehta J. Allogeneic hematopoietic stem cell transplantation in myeloma. In: Mehta J, Singhal S (eds). *Myeloma Editions*. Martin Dunitz: London, 2002; pp 349–365.
- 5 Björkstrand BB, Ljungman P, Svensson H, Hermans J, Alegre A, Apperley J *et al.* Allogeneic bone marrow transplantation versus autologous stem cell transplantation in multiple myeloma: a retrospective case-matched study from the European Group for Blood and Marrow Transplantation. *Blood* 1996; **88**: 4711–4718.
- 6 Couban S, Stewart AK, Loach D, Panzarella T, Meharchand J. Autologous and allogeneic transplantation for multiple myeloma. *Bone Marrow Transplant* 1997; **19**: 783–789.
- 7 Gahrton G, Svensson H, Cavo M, Apperley J, Bacigalupo A, Björkstrand B *et al.* Progress in allogeneic bone marrow and peripheral blood stem cell transplantation for multiple myeloma: a comparison between transplants performed 1983–1993 and 1994–1998 at European Group for Blood and Marrow Transplantation centres. *Br J Haematol* 2001; **113**: 209–216.
- 8 Barlogie B, Kyle RA, Anderson KC, Greipp PR, Lazarus HM, Hurd DD *et al.* Standard chemotherapy compared with high-dose chemoradiotherapy for multiple myeloma: final results of the Phase III US Intergroup trial S4321. *J Clin Oncol* 2006; **24**: 929–936.
- 9 Alyea E, Weller E, Schlossman R, Canning C, Webb I, Doss D *et al.* T-cell depleted allogeneic bone marrow transplantation followed by donor lymphocyte infusion in patients with multiple myeloma: induction of graft-versus-myeloma effect. *Blood* 2001; **98**: 934–939.
- 10 Lokhorst HM, Segeren CM, Verdonck LF, van der Holt B, Raymakers R, van Oers MH *et al.* Partially T-cell depleted allogeneic stem-cell transplantation for first-line treatment of multiple myeloma: a prospective evaluation of patients treated in the phase III study Hovon 24 MM. *J Clin Oncol* 2003; **21**: 1728–1733.
- 11 Mehta J, Tricot G, Jagannath S, Ayers D, Singhal S, Siegel D *et al.* Salvage autologous or allogeneic transplantation for multiple myeloma refractory or relapsing after a first autograft. *Bone Marrow Transplant* 1998; **21**: 887–892.
- 12 Libura J, Hoffman T, Passweg J, Gregor M, Favre G, Tichelli A *et al.* Graft-versus myeloma after withdrawal of immunosuppression following allogeneic peripheral stem cell transplantation. *Bone Marrow Transplant* 1999; **24**: 925–927.
- 13 Le Blanc R, Montming-Metivier S, Belanger R, Busque L, Fish D, Roy DC *et al.* Allogeneic transplantation for multiple myeloma: further evidence for a GVHD-associated graft-versus-myeloma effect. *Bone Marrow Transplant* 2001; **28**: 841–848.
- 14 Tricot G, Vesole DH, Jagannath S, Hilton J, Munshi N, Barlogie B. Graft-versus myeloma effect: proof of principle. *Blood* 1996; **87**: 1196–1198.
- 15 Verdonck L, Lokhorst H, Dekker A, Nieuwenhuis HK, Petersen EJ. Graft versus myeloma effect in two cases. *Lancet* 1996; **347**: 800–801.
- 16 Aschan J, Lonnquist B, Ringden O, Kumlien G, Gahrton G. Graft-versus myeloma effect. *Lancet* 1996; **348**: 346.
- 17 Collins RH, Shpilberg O, Drobyski W, Porter DL, Giralt S, Champlin R *et al.* Donor lymphocyte infusions in 140 patients with relapsed malignancies after allogeneic bone marrow transplantation. *J Clin Oncol* 1997; **22**: 835–843.
- 18 Lokhorst HM, Wu K, Verdonck LF, Laterveer LL, van de Donk NW, van Oers MH *et al.* The occurrence of graft versus host disease is the major predictive factor for response to donor lymphocyte infusions in multiple myeloma. *Blood* 2004; **103**: 4362–4364.
- 19 Giralt S, Aleman A, Anagnostopoulos A, Weber D, Khouri I, Anderlini P *et al.* Fludarabine/melphalan conditioning for allogeneic transplantation in patients with multiple myeloma. *Bone Marrow Transplant* 2002; **30**: 367–373.
- 20 Einsele H, Schafer HJ, Hebart H, Bader P, Meisner C, Plasswilm L *et al.* Follow-up of patients with progressive multiple myeloma undergoing allografts after reduced-intensity conditioning. *Br J Haematol* 2003; **121**: 411–418.
- 21 Peggs KS, Mackinnon S, Williams CD, D'Sa S, Thuraisundaram D, Kyriakou C *et al.* Reduced-intensity transplantation with *in vivo* T-cell depletion and adjuvant dose-escalating donor lymphocyte infusions for chemotherapy-sensitive myeloma: limited efficacy of graft-versus tumor activity. *Biol Blood Marrow Transplant* 2003; **9**: 257–265.
- 22 Perez-Simon JA, Martino R, Alegre A, Tomás JF, De Leon A, Caballero D *et al.* Chronic but not acute graft versus host disease improves outcome in multiple myeloma patients after non-myeloablative allogeneic transplantation. *Br J Haematol* 2003; **121**: 104–108.
- 23 Mohty M, Boiron JM, Damaj G, Michallet AS, Bay JO, Faucher C *et al.* Graft-versus myeloma effect following antithymocyte globulin-based reduced intensity conditioning allogeneic stem cell transplantation. *Bone Marrow Transplant* 2004; **34**: 77–87.
- 24 Gerull S, Goerner M, Benner A. Long-term outcome of non myeloablative allogeneic transplantation in patients with high-risk multiple myeloma. *Bone Marrow Transplant* 2005; **36**: 963–969.
- 25 Kroger N, Sayer HG, Schwerdtfeger R, Kiehl M, Nagler A, Renges H *et al.* Unrelated stem cell transplantation in reduced-intensity conditioning with pretransplantation antithymocyte globulin is highly effective with low transplantation-related mortality. *Blood* 2002; **100**: 3919–3924.

- 26 Crawley C, Lalancette M, Szydlo R, Gilleece M, Peggs K, Mackinnon S *et al.* Outcomes of reduced-intensity allogeneic transplantation for multiple myeloma: an analysis of prognostic factors from the Chronic Leukemia Working Party of the EBMT. *Blood* 2005; **105**: 4532–4539.
- 27 Mielcarek M, Martin PJ, Leisenring W, Flowers ME, Maloney DG, Sandmaier BM *et al.* Graft-versus-host disease after non myeloablative versus conventional hematopoietic stem cell transplantation. *Blood* 2003; **102**: 756–762.
- 28 Kroger N, Perez-Simon JA, Myint H, Klingemann H, Shimoni A, Nagler A *et al.* Relapse to prior autograft and chronic graft-versus host disease are the strongest prognostic factors for outcome of melphalan/fludarabine based dose-reduced allogeneic stem cell transplantation in patients with multiple myeloma. *Biol Blood Marrow Transplant* 2004; **10**: 698–708.
- 29 Crawley C, Iacobelli S, Björkstrand B, Apperley JF, Niederwieser D, Gahrton G. Reduced-intensity conditioning for myeloma: lower nonrelapse mortality but higher relapse rates compared with myeloablative conditioning. *Blood* 2007; **109**: 3588–3594.
- 30 Badros A, Barlogie B, Siegel E, Cottler-Fox M, Zangari M, Fassas A *et al.* Improved outcome of allogeneic transplantation in high-risk multiple myeloma patients after non-myeloablative conditioning. *J Clin Oncol* 2002; **20**: 1295–1303.
- 31 Kroger N, Schwerdtfeger R, Kiehl M, Sayer HG, Renges H, Zabelina T *et al.* Autologous stem cell transplantation followed by a dose-reduced allograft induces high complete remission rate in multiple myeloma. *Blood* 2002; **100**: 755–760.
- 32 Maloney D, Molina A, Sahebi F, Stockerl-Goldstein KE, Sandmaier BM, Bensinger W *et al.* Allografting with nonmyeloablative conditioning following cytoreductive autografts for the treatment of patients with multiple myeloma. *Blood* 2003; **101**: 3447–3454.
- 33 Attal M, Harousseau JL, Facon T, Guilhot F, Doyen C, Fuzibet JG *et al.* Single versus double autologous stem-cell transplantation for multiple myeloma. *New Engl J Med* 2003; **349**: 2495–2502.
- 34 Garban F, Attal M, Michallet M, Hulin C, Bourhis JH, Yakoub-Agha I *et al.* Prospective comparison of autologous stem cell transplantation followed by dose-reduced allograft (IFM 99–03 trial) with tandem autologous stem cell transplantation (IFM 99–04 trial) in high-risk *de novo* multiple myeloma. *Blood* 2006; **107**: 3474–3480.
- 35 Bruno B, Rotta M, Patriarca F, Mordini N, Allione B, Carnevale-Schianca F *et al.* A comparison of allografting with autografting for newly diagnosed myeloma. *New Engl J Med* 2007; **356**: 1110–1120.
- 36 Moreau P, Garban F, Facon T, Hulin C, Attal M, Benbouker L *et al.* Long-term and updated results of the IFM9903 and IFM9904 protocols comparing autologous followed by RIC-allogeneic transplantation and double transplant in high-risk *de novo* multiple myeloma. *Bone Marrow Transplant* 2007; **39** (Suppl 1): S24–S25; abstract.
- 37 Kroger N, Schilling G, Einsele H, Liebisch P, Shimoni A, Nagler A *et al.* Deletion of chromosome 13q14 detected by fluorescence *in situ* hybridization as prognostic factor following allogeneic dose-reduced stem cell transplantation in patients with multiple myeloma. *Blood* 2006; **103**: 4056–4061.
- 38 Attal M, Harousseau JL, Leyvraz S, Doyen C, Hulin C, Benbouker L *et al.* Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. *Blood* 2006; **108**: 3289–3294.
- 39 Facon T, Avet-Loiseau H, Guillermin G, Moreau P, Geneviève F, Zandeck M *et al.* Chromosome 13 abnormalities identified by FISH analysis and serum  $\beta$ 2-microglobulin produce a powerful myeloma staging system for patients receiving high-dose therapy. *Blood* 2001; **97**: 1566–1571.
- 40 Tricot G, Spencer T, Sawyer J, Spoon D, Desikan R, Fassas A *et al.* Predicting long-term ( $\geq 5$  years) event-free survival in multiple myeloma patients following planned tandem autotransplants. *Br J Haematol* 2002; **116**: 211–217.
- 41 Kroger N, Shimoni A, Zagrivnaja M, Ayuk F, Lioznov M, Schieder H *et al.* Low-dose thalidomide and donor lymphocyte infusions as adoptive immunotherapy after allogeneic stem cell transplantation in patients with multiple myeloma. *Blood* 2004; **104**: 3361–3363.
- 42 Bruno B, Patriarca F, Sorasio R, Mattei D, Montefusco V, Peccatori J *et al.* Bortezomib with or without dexamethasone in relapsed multiple myeloma following allogeneic hematopoietic cell transplantation. *Haematologica* 2006; **91**: 837–839.
- 43 Tosi P, Zamagni E, Cangini B, Tacchetti P, Perrone G, Ceccolini M *et al.* Complete remission upon bortezomib-dexamethasone therapy in three heavily pretreated multiple myeloma patients relapsing after allogeneic stem cell transplantation. *Ann Hematol* 2006; **85**: 549–558.
- 44 Van de Donk NW, Kroger N, Hegenbart U, Corradini P, San Miguel JF, Goldschmidt H *et al.* Remarkable activity of novel agents bortezomib and thalidomide in patients not responding to donor lymphocyte infusions following nonmyeloablative allogeneic stem cell transplantation in multiple myeloma. *Blood* 2006; **107**: 3415–3416.
- 45 Kroger N, Zabelina T, Ayuk F, Atanackovic D, Schieder H, Renges H *et al.* Bortezomib after dose-reduced allogeneic stem cell transplantation for multiple myeloma to enhance or maintain remission status. *Exp Hematol* 2006; **34**: 770–775.