

## Reduced intensity conditioning regimens

# Low transplant-related mortality after second allogeneic peripheral blood stem cell transplant with reduced-intensity conditioning in adult patients who have failed a prior autologous transplant

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### Summary:

Standard allogeneic stem cell transplantation (SCT) has been associated with a high transplant-related mortality (TRM) in patients who have failed a prior autologous SCT (ASCT). Reduced-intensity conditioning (RIC) regimens may reduce the toxicities and TRM of traditional myeloablative transplants. We report 46 adults who received a RIC peripheral blood SCT from an HLA-identical sibling in two multicenter prospective studies. The median interval between ASCT and allograft was 16 months, and the patients were allografted due to disease progression ( $n = 43$ ) and/or secondary myelodysplasia ( $n = 4$ ). Conditioning regimens consisted of fludarabine plus melphalan ( $n = 41$ ) or busulphan ( $n = 5$ ). The 100-day incidence of grade II–IV acute graft-versus-host disease (GVHD) was 42% (24% grade III–IV), and 10/30 evaluable patients developed chronic extensive GVHD. Early complete donor chimerism in bone marrow and peripheral blood was observed in 35/42 (83%) patients, and 16 evaluable patients had complete chimerism 1 year post transplant. With a median follow-up of 358 days (450 in 29 survivors), the 1-year incidence of TRM was 24%, and the 1-year overall (OS) and progression-free survival were 63% and 57%, respectively. Patients who had chemorefractory/progressive disease, a low performance status or received GVHD prophylaxis with cyclosporine A alone ( $n = 32$ ) had a 1-year TRM of 35% and an OS of 46%, while patients who had none of these characteristics ( $n = 32$ ) had a 1-year TRM of 35% and an OS of 46% while patients who had none of these characteristics ( $n = 14$ ) had a TRM of 0% and an OS of 100%. Our results suggest that adult patients who fail a prior ASCT can be salvaged with a RIC allogeneic PBSCT with a low

risk of TRM, although patient selection has a profound influence on early outcome.

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Autologous hematopoietic stem cell transplantation (ASCT) is currently a widely used treatment modality for patients with high-risk non-Hodgkin's lymphoma (NHL), Hodgkin's disease (HD), multiple myeloma (MM) and acute leukemia. In 1999 nearly 15 000 ASCT were performed in Europe alone.<sup>1</sup> Transplant-related mortality (TRM) is low after autologous transplants, usually <5% in most centers and disease categories, where the main cause of treatment failure is relapse of the underlying malignancy, and in recent years, the development of secondary myelodysplasia or acute myeloid leukemia (AML) in heavily pre-treated patients. Allogeneic SCT, on the other hand, carries a lower risk of disease recurrence, but has a much higher early TRM. TRM is especially high in elderly patients and in those who have received a prior ASCT. In adults, the 1-year TRM following a conventional (ie myeloablative) allogeneic SCT in recipients of a prior autograft has been reported as high as 50–85%,<sup>2–7</sup> making this salvage strategy of limited success in the majority of patients. In recent years several groups of investigators have developed reduced-intensity conditioning (RIC) regimens, which lead to engraftment of donor lymphoid and hematopoietic stem cells without the extrahematologic toxicities of traditional myeloablative transplants.<sup>8–12</sup> This reduced toxicity may make these RIC regimens especially suitable for patients with a high risk of TRM, in particular recipients of second transplants or those with severe comorbid diseases.<sup>10</sup> We herein report the results of second RIC allogeneic peripheral blood stem cell transplants (PBSCT) after a failed autograft in adults included in two prospective multicenter studies conducted in Spain.

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## Patients and methods

This study includes 46 adults who were recruited in two multicenter prospective studies of RIC allogeneic PBST that have been conducted in Spain since early 1999. In both protocols, a prior autologous HSCT was an inclusion criterion. Exclusion criteria were severe comorbid organ dysfunction and a very low performance status. Patients gave written informed consent for inclusion in the specific protocol, which was approved by all local ethical review boards and the Spanish Drug Agency. Details of both protocols have been previously described in detail.<sup>13,14</sup>

Patient characteristics at the time of the first and second transplant are shown in Table 1. The median age was 47 years (range, 19–64) and there were 24 males and 22 females. Disease phase at the time of ASCT was categorized as early in 15 cases (acute leukemia in first complete remission and poor-risk lymphoid malignancy, including multiple myeloma, in first remission), intermediate in 27 patients (acute leukemia in second or higher complete remission and lymphoid malignancy in second or higher remission) and advanced in four cases (refractory or relapsed acute leukemia and relapsed or progressive lymph-

oid malignancy). Forty patients had relapsed at a median of 10 months (range, 1–83) after the ASCT, while three patients had developed a secondary myelodysplastic syndrome (MDS) 20 to 56 months after the ASCT, without disease progression; one patient had both a secondary MDS and relapsed follicular lymphoma at the time of the RIC allograft. Following salvage therapy in 37 patients before the RIC allograft, 21 (46%) were in partial or complete remission, while 16 (35%) had progressive chemorefractory disease; nine patients were not treated before the second transplant but had stable non-progressive disease. The interval between transplants ranged from 3 to 83 months (median 16), with less than 1 year between them in 20 (44%) patients. At transplant, 27 patients (59%) had a Karnofsky performance status of 80%.

All but one donor/recipient pair were seropositive for cytomegalovirus (CMV) IgG pre-transplant, and in 21 cases (46%) a sex difference was present between donor and recipient, with seven males receiving a transplant from a female donor. All donors were HLA-identical siblings, as determined by serology for class I antigens and high-resolution DNA typing for DRB1 and DQB1.

### Conditioning regimens

Three RIC regimens were allowed. In all cases fludarabine 30 mg/m<sup>2</sup> i.v. for 5 consecutive days (–8 to –4 or –9 to –5) was used. Additionally, patients received either melphalan at a dose of 70 mg/m<sup>2</sup> i.v. on days –3 and –2 (total 140 mg/m<sup>2</sup>) (*n* = 27) or 80 mg/m<sup>2</sup> i.v. on day –2 (*n* = 14), or busulphan 1 mg/kg × 10 doses (days –6 to –4, total 10 mg/kg) (*n* = 5), with phenytoin given as anticonvulsant prophylaxis. Unmanipulated PBST were infused on day 0.

### Graft-versus-host disease (GVHD) prophylaxis and supportive care

GVHD prophylaxis consisted of cyclosporin A (CsA) plus short-course methotrexate (MTX) in most cases (*n* = 39); the first seven patients included in one protocol received CsA alone, but MTX was added later on after the first 6/15 (40%) patients in that study developed lethal grade III–IV acute GVHD.<sup>14</sup> CsA was given from before day 0 at a dose adjusted to maintain the blood levels in the therapeutic range (150–350 µg/l) until tapering. In the event that acute GVHD grade >I did not develop, CsA was tapered 10% weekly starting on day +90 and discontinued by day +150, if no GVHD appeared. MTX was given at a dose of 10 mg/m<sup>2</sup> i.v. on days +1, +3 and +6, followed by folinic acid rescue at a dose of 10 mg i.v. every 6 h for four doses starting 24 h after each dose of MTX.

Infection prophylaxis consisted of norfloxacin or ciprofloxacin during the neutropenic period, fluconazole until hospital discharge and whenever steroids were used, standard-dose acyclovir (800 twice a day by mouth or 400 mg twice a day i.v.), and bactrim 2 or 3 days per week from engraftment and until day +180. CMV antigenemia was monitored at least once weekly during the first 3 months post-transplant and then as clinically indicated. Febrile neutropenia was managed by standard methods according to each institution's protocol.

**Table 1** Patient characteristics (*n* = 46) (% in parentheses)

Age, median (range)	47 years (19–64)
Sex (M / F)	24/22
Underlying disease at second transplant	
Multiple myeloma	14 (30)
Non-Hodgkin's lymphoma	16 <sup>a</sup> (35)
Hodgkin's disease	9 (20)
Acute myelogenous leukemia	3 (7)
Secondary myelodysplastic syndrome	4 <sup>a</sup> (9)
Chronic lymphocytic leukemia	1
Disease phase at ASCT	
Early	15 (33)
Intermediate	27 (59)
Advanced	4 (9)
Conditioning for prior ASCT	
TBI-containing regimen	9 (20)
BEAM/CBV	24 (52)
Other chemotherapy-only regimens	13 (28)
Remission duration after ASCT, median months (range)	10 (1–83)
Disease status at second transplant	
Untreated before transplant <sup>b</sup>	9 (20)
Progressive disease (chemorefractory)	16 (35)
Chemosensitive status	21 (46)
Complete remission	6
Partial remission	15
Interval between transplants, median months (range)	16 (3–83)
<6 months	7 (15)
6–12 months	13 (28)
>12 months	26 (57)

ASCT = autologous hematopoietic stem cell transplantation; TBI = total body irradiation; BEAM = BCNU, etoposide, Ara-C and melphalan; CBV = cyclophosphamide, BCNU and etoposide.

<sup>a</sup>Myelodysplastic syndrome (MDS) following an autologous transplant for follicular lymphoma in three cases and mantle-cell lymphoma in one case. One patient had both secondary MDS and relapsed follicular lymphoma at second transplant, while the other three were in remission from their lymphoma.

<sup>b</sup>Non-progressive malignancy at the time of the reduced-intensity conditioning allograft.

Acute and chronic GVHD were graded by established criteria.<sup>15</sup> Grade II or greater acute GVHD was treated with prednisone or an equivalent at 2 mg/kg/day, with subsequent tapering in responsive cases. Refractory GVHD was treated with antilymphocyte globulin or other salvage regimens.

### Chimerism analysis

After transplant, serial samples of peripheral blood (PB) and bone marrow (BM) mononuclear cells were analyzed for degrees of donor–recipient chimerism using PCR of informative minisatellite regions following each center’s standard methods. The sensitivity of all methods used was reported to be between 1% and 5% donor-derived cells by all participating centers,<sup>13,14</sup> and thus mixed chimerism is defined as >1% to 5% donor-derived cells in the sample analyzed, while the presence of 100% donor-derived DNA is considered complete donor chimerism.

### Statistical analysis

Probabilities of overall survival (OS) and progression-free survival (PFS) were estimated from the time of transplantation using Kaplan–Meier product-limit estimates, while the probabilities of TRM and disease progression were calculated using cumulative incidence estimates.<sup>16</sup> For the endpoint of progression, TRM was regarded as a competing risk, whereas disease progression was regarded as a competing risk for TRM. Disease progression was defined as re-emergence of the underlying disease (if a complete remission had been reached) or increase from a prior stable condition. Patients who died without disease progression were categorized as TRM, while patients alive without progression were censored at last follow-up and those who suffered disease progression were censored at progression. OS was calculated from transplant until death from any cause, and surviving patients were censored at last followup. The cumulative incidence and time to onset of acute GVHD were calculated in all patients who survived for at least 14 days after transplant.

Univariate analyses of the association of various clinical risk factors with the hazard of failure from TRM were performed using Cox regression models. Factors examined included age at second transplant (as a continuous variable and as <45 vs ≥45 years), sex, sex mismatch, time from first to second transplant (as a continuous variable and as <12 vs ≥12 months), phase of disease at second transplant (untreated or remission/chemosensitive disease vs progressive/chemorefractory disease), preparative regimen for prior ASCT (TBI-containing vs chemotherapy-only) and Karnofsky performance status at second transplant (≤ 80% vs >80%). Due to the small sample sizes and the few TRM events, multivariate analysis was not carried out. Two-sided *P* values resulting from the regression models were derived using the Wald test, and no adjustments were made for multiple comparisons.

## Results

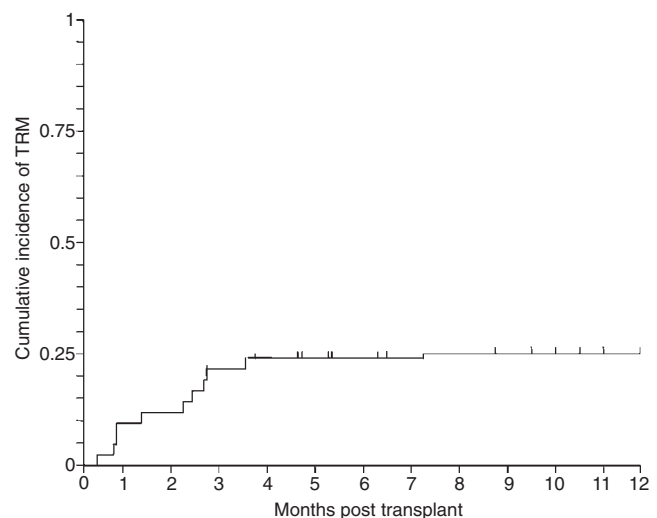
### Toxicity and TRM

Apart from transient nausea in some patients, the preparative regimens were generally well tolerated. Two patients (4%) died early, before engraftment, due to toxicity attributable to the conditioning regimen (one from hepatic VOD and one from multiorgan failure).

Seventeen patients have died, six from the underlying disease and 11 from TRM; four patients died primarily from GVHD, five from infection (one of whom also had uncontrolled GVHD) and these were two early deaths. The 100-day and 1-year cumulative incidences of TRM were 20% (95% CI, 11% to 35%) and 24% (95% CI, 15% to 41%), respectively (Figure 1). Univariate Cox regression analyses of the risk of TRM according to various pretransplant clinical variables found a higher risk of TRM in patients with progressive/chemorefractory disease (*n* = 16) vs those with untreated disease or in remission at transplant (*n* = 30) (Hazard ratio (HR) 5.8 (95% CI 1.5–22), *P* = 0.009), in those who received GVHD prophylaxis with CsA alone (*n* = 7) (HR 4.6 (95% CI 1.4–15), *P* = 0.01) and a Karnofsky performance status at second transplant ≤80% (*n* = 26) (HR 8.2 (95% CI 1.1–64.3), *P* = 0.04). Other variables analyzed did not influence TRM (see Statistical methods). As stated earlier, multivariate analysis was not performed. Since it is probable that disease status and performance status (and maybe GVHD prophylaxis) may be related variables, we classified the patients who had any of these three variables as at high risk for TRM (*n* = 32), whereas those who had none were classified as the low-risk group (*n* = 14). The low-risk group had a 0% incidence of TRM, while the high-risk group had a 1-year TRM incidence of 35% (95% CI 22–56%) (*P* < 0.01).

### Hematologic recovery, infections and chimerism

The infused allograft contained a median of  $5.6 \times 10^6$  CD34<sup>+</sup> cells/kg (range, 2.7–14.5) and  $310 \times 10^6$  T cells/kg



**Figure 1** Cumulative incidence of transplant-related mortality (TRM). The 1-year estimated TRM was 24% (95% CI, 15% to 41%).

(range, 60–930). Hematologic recovery was prompt in all but the two early deaths. Neutrophils decreased to  $<0.5 \times 10^9/l$  in all cases and recovered at a median of day +14 (range, +10 to +34), and median time to reach a stable platelet count  $>20 \times 10^9/l$  was day +11 (range, +8 to +42). Thirty-three patients (72%) developed febrile neutropenia which required i.v. broad-spectrum antibiotics. Early infections included four cases of uncomplicated bacteremia and two cases of pneumonia, one of which was fatal. Late infections included two cutaneous varicella herpes-zoster infections, one case of adenovirus pneumonia, one influenzae A pneumonia and one pneumonia of unknown etiology. Only six patients developed CMV infection, including one possible CMV pneumonia.

On days +21 to +28, 24/29 (83%) patients tested showed a pattern of complete donor chimerism in BM and 32/38 (84%) patients in PB (overall 35/42 (83%) complete chimerism). The proportion of patients with complete donor chimerism increased on days +90 to +100 (24/26 (92%) in BM and 26/28 (93%) in PB), at 6 months (17/18 (94%) in BM and 17/17 (100%) in PB) and at 1 year (16/16 (100%) in BM and 13/13 (100%) in PB).

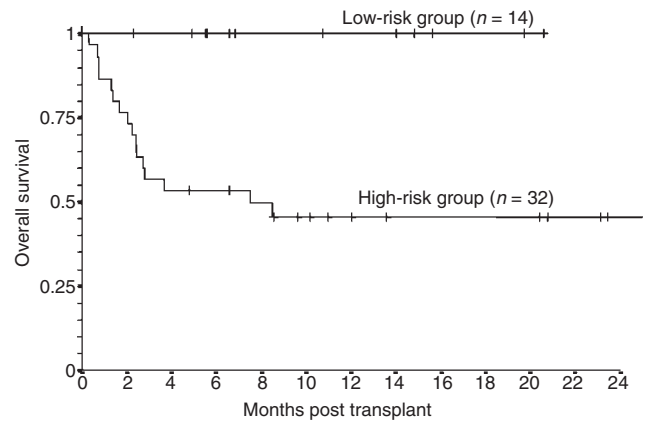
#### Acute and chronic GVHD

Acute GVHD grade  $\geq$ II occurred in 18 patients, for a 100-day cumulative incidence of 42% (95% CI, 30% to 59%), and the incidence of grade III–IV acute GVHD was 24% (95% CI, 14% to 42%). The median day of onset was +23 (range, +7 to +66), while patients were receiving therapeutic doses of CsA. Six of seven patients (86%) who received CsA prophylaxis and 12/37 (32%) evaluable patients who received CsA/MTX developed acute GVHD grade  $\geq$ II ( $P = 0.01$ ). GVHD was directly implicated in the patients' death in three of seven (43%) and two of 37 (5%) cases, respectively ( $P = 0.01$ ). Twenty-two of 30 evaluable patients developed chronic GVHD, which was extensive in 10 cases.

#### Responses and outcome

Currently 29 patients are alive, with a median follow-up of 450 days (range, 100–853); one patient is alive after disease progression, while 28 are alive in complete remission ( $n = 19$ ) or in partial remission/stable disease ( $n = 9$ ). The 1-year OS and PFS were 63% (95% CI, 50% to 77%) and 57% (95% CI, 43% to 71%), respectively. The OS for high-risk patients was 46% (95% CI 30% to 62%) while it was 100% in low-risk patients ( $P = 0.001$ ) (Figure 2). The respective probabilities of PFS were 46% (30% to 62%) and 89% (67% to 100%) ( $P = 0.007$ ). The cumulative incidence of disease progression was 23% (95% CI 13% to 49%). The incidences in high and low-risk groups were 28% (95% CI, 15% to 52%) and 10% (95% CI, 5% to 53%) ( $P = 0.5$ ), respectively. Table 2 shows the outcomes according to disease categories.

**Lymphoid malignancies:** Pre-transplant 35/40 patients had measurable disease, as seen in Table 2. At day +100 post-transplant, 10 of these patients were in CR, possibly reflecting disease response to the chemotherapy given in



**Figure 2** Overall survival (OS) after the second reduced-intensity allogeneic PBSCT. Comparison of the OS in patients in the low-risk group (100%) and in the high-risk group (46%) ( $P = 0.001$ ). High-risk patients were those with one or more of the following characteristics: GVHD prophylaxis with cyclosporin A alone, progressive/chemorefractory disease at transplant and/or Karnofsky performance status  $\leq$ 80% at transplant.

the RIC regimen. At last follow-up, four of 14 of those who still had measurable disease on day +100 had entered into CR, and this may be due to a graft-versus-tumor effect. Five patients progressed after transplant, while 11 (28%) died without disease progression.

#### Discussion

Adult patients with leukemia or lymphoma who fail an ASCT generally have a very poor short-term prognosis. Allogeneic SCT using conventional myeloablative conditioning has been used to salvage some of these patients, although the high early TRM (50–85%) has precluded most patients from benefiting from a possible graft-versus-tumor effect.<sup>2–7</sup> This scenario is thus ideal for testing the potential of RIC regimens in inducing antitumor responses if these protocols can indeed reduce the early TRM and allow for sustained donor chimerism. Our results suggest that the TRM can indeed be lowered in this setting, and that donor chimerism is systematically achieved and maintained over time. Although it is too early to determine the potential benefit of any graft-versus-tumor effect associated with this sustained engraftment, the 1-year OS of 63% and 57% PFS in these advanced malignancies appear promising. Other authors have found relatively low early TRM following a RIC allograft in patients who have failed a prior ASCT. Several small series had non-relapse mortalities in two of five,<sup>17</sup> two of 10,<sup>18</sup> one of 12<sup>19</sup> and three of 16 patients,<sup>20</sup> usually from GVHD-related complications. In the largest prior study, Kottaridis *et al*<sup>21</sup> found a 16% 1-year probability of TRM among 45 consecutive patients included in a UK collaborative study. Of note is the fact that these authors used a preparative regimen similar to ours, except for the addition of CAMPATH-1H, an antilymphocyte antibody that produces *in vivo* T cell depletion and virtually eliminates the risk of moderate-to-severe GVHD. This strategy thus eliminates GVHD-related deaths, but if further immune-manipulation is not used it may also hamper the

**Table 2** Disease outcome after the second RIC allograft

	Number patients	Pretransplant status				Median f/u (days)	Status at day +100				Status at last follow-up			
		CR	PR	Refr	UT		CR	SD	PD	TRM	CR	DS	PD	TRM
Non-Hodgkin's lymphoma	16 <sup>a</sup>	3	5	6	2	375	9	1	3	3	8	—	4	4
Follicular lymphoma	8	1	4	2	1		5	1	—	2	6	—	—	2
Aggressive lymphoma <sup>c</sup>	8	2	1	4	1		4	—	3	1	2	—	4	2
Multiple myeloma	14	1	9	4	—	365	3	9	—	2	3	8	—	3
Hodgkin's disease	9	1	1	5	2	326	3	2	—	4	4	—	1	4
Acute myelogenous leukemia	3	1	—	—	2	224	1	—	2	—	1	—	2	—
Secondary MDS	4 <sup>a</sup>	—	—	—	4	590	4	—	—	—	4	—	—	—
Chronic lymphocytic leukemia	1	—	—	1	—	100	—	1	—	—	—	1	—	—
Total	46	6	15	16	9	378 <sup>b</sup>	19	13	5	9	19	9	7	11

f/u = follow-up in days; CR = complete remission; PR = partial remission; Refr = refractory to prior chemotherapy; UT = untreated prior to transplant; SD = stable disease; PD = progressive disease; TRM = transplant-related mortality; MDS = myelodysplastic syndrome.

<sup>a</sup>One patient had both untreated secondary MDS and relapsed follicular lymphoma at second transplant.

<sup>b</sup>The median follow-up for the 29 survivors was 450 days (range, 100–853).

<sup>c</sup>Includes four cases of diffuse large B cell lymphoma and four cases of peripheral T cell lymphoma.

antitumor effect of the RIC allograft by avoiding a graft-versus-tumor effect.

Of special interest in our study is that we were able to establish risk groups for TRM and OS based on simple clinical variables. Not surprisingly, most patients (32/46, 70%) fell into the high-risk group. Nevertheless, there were marked differences in both TRM and OS between both risk groups; these differences were due to a lower TRM in the low-risk group, since there were no apparent differences between groups in the incidence of disease progression post-transplant. However, even in our high-risk patient group, the 46% 1-year PFS appears very promising.

These data suggest that maintaining an acceptable performance status, using optimal GVHD prophylaxis and controlling the underlying disease before a RIC allograft in patients who fail an ASCT will probably improve the chances of short-term success by lowering the TRM and allowing further time for the onset of a graft-versus-tumor effect. This observation also explains the low early TRM (<10%) observed in tandem planned ASCT followed by a RIC allogeneic transplant.<sup>22</sup>

In summary, our results suggest that adult patients who fail a prior ASCT can be salvaged with a RIC allogeneic PBSCT with a low risk of early TRM. Patient selection and having a non-progressive malignancy at transplant will, however, have an impact on TRM, and further efforts to reduce the TRM in high-risk patients should be sought.

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## References

- 1 Gratwohl A, Passweg J, Baldomero H, Urbano-Ispizua A for the European Group for Blood and Marrow Transplantation (EBMT). Hematopoietic stem cell transplantation in Europe 1999. *Bone Marrow Transplant* 2001; **27**: 899–916.
- 2 Di Grazia C, Raiola AM, Van Lint MT *et al*. Conventional hematopoietic stem cell transplantation from identical or alternative donors are feasible in recipients relapsing after an autograft. *Haematologica* 2001; **86**: 646–651.
- 3 Rowlings PA, Greenstein V, Nivison-Smith I *et al*. Second allogeneic transplant for leukaemia after a failed first autologous transplant. *Blood* 2000; **96**: 197a (Abstr.).
- 4 Kulkarni S, Powles RL, Treleaven JG *et al*. Impact of previous high-dose therapy on outcome after allografting for multiple myeloma. *Bone Marrow Transplant* 1999; **23**: 675–680.
- 5 Ringdén O, Labopin M, Gorin NC *et al*. The dismal outcome in patients with acute leukemia who relapse after an autograft is improved if a second autograft or a matched allograft is performed. *Bone Marrow Transplant* 2000; **25**: 1053–1058.
- 6 Radich JP, Gooley T, Sanders JE *et al*. Second allogeneic transplantation after failure of first autologous transplantation. *Biol Blood Marrow Transplant* 2000; **6**: 272–279.
- 7 Tsai T, Goodman S, Saez R *et al*. Allogeneic bone marrow transplantation in patients who relapse after an autologous transplantation. *Bone Marrow Transplant* 1997; **20**: 859–863.
- 8 Giralt S, Thall PF, Khouri I *et al*. Melphalan and purine analog-containing preparative regimens: reduced-intensity conditioning for patients with hematologic malignancies undergoing allogeneic progenitor cell transplantation. *Blood* 2001; **97**: 631–637.
- 9 Slavin S, Nagler A, Naparstek E *et al*. Non-myeloablative stem cell transplantation and cell therapy as an alternative to conventional bone marrow transplantation with lethal cytoreduction for the treatment of malignant and nonmalignant hematologic diseases. *Blood* 1998; **91**: 756–63.
- 10 Carella AM, Champlin R, Slavin S *et al*. Mini-allografts: ongoing trials in humans. *Bone Marrow Transplant* 2000; **25**: 345–350.
- 11 McSweeney PA, Niederwieser D, Shizuru JA *et al*. Hematopoietic cell transplantation in older patients with hematologic

- malignancies: replacing high-dose cytotoxic therapy with graft-versus-tumor effects. *Blood* 2001; **97**: 3390–3400.
- 12 Kottaridis PD, Milligan DW, Chopra R *et al*. *In vivo* CAMPATH-1H prevents graft-versus-host disease following non-myeloablative stem cell transplantation. *Blood* 2000; **96**: 2419–2425.
  - 13 Martino R, Caballero MD, Canals C *et al*. Allogeneic peripheral blood stem cell transplantation with reduced-intensity conditioning: results of a prospective multicenter study. *Br J Haematol* 2001; **115**: 653–659.
  - 14 De la Serna J, Hernández-Maraver MD, Díez JL *et al*. Allogeneic hematopoietic progenitor cell transplantation after non-myeloablative conditioning: results of a multicenter study (Spanish). *Methods Find Exp Clin Pharmacol* 2001; **23**: 103–108.
  - 15 Przepiorka D, Weisdorf D, Martin P *et al*. 1994 consensus conference on acute GVHD grading. *Bone Marrow Transplant* 1995; **15**: 825–830.
  - 16 Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimations. *Stat Med* 1999; **18**: 695–706.
  - 17 Dreger P, Glass B, Seyfarth B *et al*. Reduced-intensity allogeneic stem cell transplantation as salvage treatment for patients with indolent lymphoma or CLL after failure of autologous SCT. *Bone Marrow Transplant* 2000; **26**: 1361–1363.
  - 18 Dey BR, McAfee S, Sackstein R *et al*. Successful second allogeneic marrow transplantation following non-myeloablative conditioning for patients with relapsed/refractory lymphoma after failure of autologous transplant. *Blood* 2000; **96**: 412a (Abstr.).
  - 19 Nagler A, Or R, Naparstek E *et al*. Second allogeneic stem cell transplantation using nonmyeloablative conditioning for patients who relapsed or developed secondary malignancies following autologous transplantation. *Exp Hematol* 2000; **28**: 1096–1104.
  - 20 Badros A, Barlogie B, Morris C *et al*. High response rate in refractory and poor-risk multiple myeloma after allotransplantation using a nonmyeloablative conditioning regimen and donor lymphocyte infusions. *Blood* 2001; **97**: 2574–2579.
  - 21 Kottaridis PD, Milligan DW, Mahendra P *et al*. Non-myeloablative conditioning limits transplant-related mortality in patients who have previously failed high-dose treatment. *Blood* 2000; **96**: 553a (Abstr.).
  - 22 Carella AM, Giralt S, Slavin S. Nonmyeloablative therapy with allogeneic hematopoietic stem cell transplantation as treatment of hematological neoplasia. *Haematologica* 2000; **85**: 304–313.