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Allogeneic stem cell transplantation with fludarabine-based, less intensive conditioning regimens as adoptive immunotherapy in advanced Hodgkin's disease

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Summary:

Six patients with advanced Hodgkin's disease in which multiple conventional treatments (median prior chemotherapy regimens: seven), radiation therapy, and a prior autologous stem cell transplantation (SCT) had failed underwent allogeneic SCT following a fludarabine-based conditioning regimen. Median age was 29 years (22–30). Median time to progression after autologous SCT was 6 months (4–21). Disease status at transplant was refractory relapse (n = 3) and sensitive relapse (n = 3). Cell source was filgrastim-mobilized peripheral blood stem cells from an HLA-identical sibling (n = 4) or matched unrelated donor marrow (n = 2). Conditioning regimens were fludarabine–cyclophosphamide–antithymocyte globulin (n = 4), fludarabine–melphalan (n = 1) and fludarabine–cytarabine–idarubicin (n = 1). Myeloid recovery was prompt, with an absolute neutrophil count $\geqslant$500/μl on day 12 (11–15). Median platelet recovery to $\geqslant$20 000/μl was on day 9 (0–60). Chimerism studies on day 30 indicated 100% donor-derived hematopoiesis in 4/5 evaluable patients (4/4 non-progressors). All responders (3/3) have ongoing 100% donor-derived chimerism. Acute graft-versus-host disease (GVHD) was diagnosed in 4/6 evaluable patients. Chronic GVHD was present in 2/4 evaluable patients. There were no regimen-related deaths. Overall day 100 transplant-related mortality was 2/6 (33%). Three patients have expired and three are alive and progression-free with a median follow-up of 9 months (6–26) post transplant. We conclude that allogeneic stem cell transplantation with fludarabine-based preparative regimens is feasible in these high-risk, heavily pretreated HD patients. *Bone Marrow Transplantation* (2000) **26,** 615–620.

Keywords: Hodgkin's disease; Hodgkin's lymphoma; allogeneic stem cell transplantation; bone marrow transplantation; peripheral blood stem cell transplantation; granulocyte colony-stimulating factor

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Most patients with Hodgkin's disease (HD) are successfully treated with chemotherapy and/or radiation therapy. Recurrences can often be salvaged with high-dose chemotherapy and autologous stem cell transplantation.[1–3] The role of allogeneic stem cell transplantation (SCT) in the management of HD is controversial. Published experience is largely limited to registry data or experience from large transplant centers. The vast majority of patients included were extensively pretreated and had advanced, chemoresistant disease. Despite high rates of transplant-related mortality (TRM) (50–60%), a subset of patients (15–20%) achieved durable remissions. A major factor contributing to the TRM was regimen-related toxicity.[4–6]

The presence of a graft-versus-Hodgkin's effect was postulated in some of these reports,[5,6] raising the possibility that the outcome could be significantly more favorable in patients transplanted earlier in the course of their disease and/or with less intensive preparative regimens. Allogeneic SCT following less intensive, non-myeloablative conditioning regimens is yielding very promising preliminary results in several hematological malignancies.[7,8] We elected to explore the feasibility of a similar approach in patients with advanced HD. The preliminary results of this pilot study are presented here.

Patients and methods

Patient population

All patients with relapsed HD who underwent allogeneic SCT at the University of Texas MD Anderson Cancer Center (UT-MDACC) following conditioning with a fludarabine-based preparative regimen are included in this report. Outside pathologic material was reviewed at UT-MDACC. Patients were deemed eligible for allotransplantation if they had chemosensitive or stable (ie nonprogressive) disease after salvage chemotherapy, no active or uncontrolled infection as well as adequate cardiac, pulmonary, renal and hepatic function. Patients needed to have a related donor, either fully matched or one-antigen mismatched, or a fully matched unrelated donor willing and capable of donating filgrastim-mobilized peripheral blood

stem cells (PBSCs: fully matched related donors) or bone marrow (unrelated donors).

The treatment plan for these patients was approved by the Institutional Review Board of the UT-MDACC. Both patients and donors were required to sign written informed consent. Unrelated donors were recruited, consented and harvested through the National Marrow Donor Program (NMDP) according to established NMDP procedures.

Conditioning regimens

The conditioning regimen in this pilot study (employed in four patients) included fludarabine (25 mg/m^2 intravenously daily for 5 days), cyclophosphamide (1 g/m^2 intravenously daily for 3 days) and antithymocyte globulin (20 mg/kg intravenously daily for 3 days) (FC-ATG). Two additional patients received fludarabine-based conditioning and are also included in this report. One patient (UPN 3032) received fludarabine (25 mg/m^2 intravenously daily for 5 days) and melphalan (90 mg/m^2 intravenously daily for 2 days) as part of a prior protocol (FM). One patient (UPN 3961) received fludarabine (30 mg/m^2 intravenously daily for 4 days), cytarabine (2 g/m^2 daily for 4 days), idarubicin (12 mg/m^2 intravenously daily for 3 days) (FLAG-IDA) in view of a coexistent therapy-related myelodysplasia.

Post-transplant immunosuppression

All patients received either cyclosporine or tacrolimus intravenously beginning 2 days before transplantation, dosed to maintain therapeutic serum levels (4–12 ng/ml for tacrolimus and 200–300 ng/ml for cyclosporine) and switched to oral administration as soon as oral intake was feasible. Methotrexate (5 mg/m^2 intravenously) was administered on days 1, 3, 6 and (for the unrelated donor transplants) 11 post transplant.

Supportive care

Antibacterial, antifungal and antiviral prophylaxis followed institutional protocols. This included trimethoprim–sulfamethoxazole for *Pneumocystis carinii* prophylaxis, fluconazole for antifungal prophylaxis, acyclovir for antiviral prophylaxis and penicillin with an oral quinolone for antibacterial prophylaxis. Cytomegalovirus (CMV) prophylaxis consisted of weekly or bi-weekly surveillance blood CMV cultures using shell vial and rapid antigen techniques, with ganciclovir therapy instituted on the basis of positive assays. Recipients of unrelated donor transplants received ganciclovir as primary CMV prophylaxis until day 100. All patients also received filgrastim 5 μg/kg subcutaneously daily beginning on day 7 post transplant until they reached an absolute neutrophil count (ANC) $\geqslant$1000/μl for 3 consecutive days. All blood products were filtered and irradiated prior to transfusion.

Criteria for study evaluation

Day 0 was the stem cell infusion day. Engraftment was defined as the first of 3 consecutive days of an ANC $\geqslant$500/μl. Platelet recovery was considered to have occurred on the first of 7 consecutive days of an unsupported platelet count $\geqslant$20 000/μl. Patients were evaluable for engraftment if they survived at least 30 days following their transplant. Chimerism was determined, beginning on day 30 post transplant, on bone marrow samples by standard cytogenetics (in the event of a donor–recipient sex mismatch) or restriction fragment length polymorphism (RFLP) and, more recently, with PCR-based microsatellite polymorphism analysis using established criteria.[9]

Regimen-related toxicity (RRT) was graded according to the Bearman criteria.[10] Acute and chronic graft-versus-host disease was graded according to established criteria.[11,12] Patients were considered evaluable for acute GVHD if they had survived at least 40 days after transplant and for chronic GVHD if they had survived at least 80 days. Epstein–Barr virus status of the tumor was established by immunohistology for the EBV latent membrane protein (LMP-1) on tissue or archival samples of paraffin-embedded tissue.[13]

Response definitions

A complete remission (CR) was defined as disappearance of all clinical and radiological evidence of active disease for a minimum of 8 consecutive weeks. Complete remission, unconfirmed/uncertain (CRU) was defined as the presence of residual radiographic abnormalities of unclear clinical significance, unchanged or decreased in size during an observation period of least 8 weeks and non-gallium avid (if initially gallium positive).

A sensitive relapse was defined as the achievement of at least a partial response (defined as at least a 50% decrease in the sum of the products of diameters of any measured lesions persisting for at least 4 weeks) to salvage chemotherapy, whereas patients failing to meet this definition qualified as refractory relapses.

The response to treatment was evaluated beginning on day 100 post transplant, with a reassessment including physical examination and imaging studies every 2–3 months afterwards. In the event of CRU, the day 100 response was evaluated retrospectively. Progressive disease was defined as the presence of clinical and radiological evidence of disease progression, either post transplant or while receiving salvage chemotherapy pretransplant.

Statistical endpoints

In keeping with the pilot study design, main endpoints were engraftment (ie neutrophil and platelet recovery as well as chimerism), GVHD, regimen-related toxicity and overall early transplant-related mortality. Secondary endpoints were disease response and survival.

Results

Patient characteristics

Patient demographics and characteristics are displayed in Table 1. The median age at transplant was 29 years (22–30). The median number of chemotherapy regimens

Table 1 Patient demographics, histological diagnosis and treatment history

UPN	*Age/ Sex*	*HD histology type*	*EBV status*	*Time from diagnosis to allogeneic SCT (months)*	*No of relapses*	*No of prior chemotherapy regimens*	*Prior radiation therapy*	*Prior autologous SCT (conditioning)*	*Time to progression after autologous SCT (months)*	*Disease status (stage) at transplant*
2880	29/M	Nodular sclerosis	Negative	74	4	8	Yes (neck, left axilla, mediastinum)	Yes (CBV)	4	Sensitive Relapse (II)
2957	29/M	Nodular sclerosis	Unknown	60	2	9	Yes (mantle)	Yes (Bu-Cy)	6	Refractory Relapse (II)
3032	22/M	Lymphocyte predominant	Negative	80	6	5	Yes (mantle)	Yes (CBV)	7	Sensitive Relapse (II)
3588	30/M	Nodular sclerosis	Unknown	73	3	7	Yes (mantle)	Yes (By-Cy)	4	Refractory Relapse (IV)
3837	29/M	Nodular sclerosis	Unknown	37	2	7	Yes (mantle)	Yes (CBV)	6	Refractory Relapse (IV)
3961	30/F	Non-further specified	Negative	52	2	5	Yes (mantle)	Yes (Cy-TT)	21	Sensitive Relapse (III)

UPN = Unique patient number; HD = Hodgkin's disease; EBV = Epstein–Barr virus; SCT = stem cell transplant; Bu-Cy = busulfan–cyclophosphamide; CBV = cyclophosphamide–BCNU–etoposide; Cy-TT = cyclophosphamide–thiotepa.
HD staging as described previously.[2]
UPN 3961 had a concomitant therapy-related myelodysplasia.

received prior to allogeneic transplant was seven (5–9), and all patients had received prior radiotherapy. All patients had undergone a prior autologous bone marrow/stem cell transplant. The median time interval between the autologous and the allogeneic SCT was 20 months (13–46). The median time to progression after autologous SCT was 6 months (4–21).

One patient (UPN 3961) had a coexistent therapy-related myelodysplasia (tMDS) with a del (20q) karyotypic abnormality. The median time from diagnosis to allogeneic SCT was 66 months (37–80). None of the patients was HIV positive.

Of the three patients whose pathologic material could be retrieved for EBV testing, all (3/3) proved to be negative on LMP-1 immunostaining.

Stem cell source

PBSCs were employed in four patients and bone marrow in two (Table 2). The median $CD34^+$ cell dose was 4.6×10^6/kg (3.6–7.3).

Engraftment and GVHD

Hematological recovery data are presented in Table 2. In three patients the platelet count never dropped below 20 000/μl after the conditioning regimen.

Chimerism data at day 30 (Table 2) indicate 100% donor-derived engraftment in 4/5 evaluable patients (4/4 nonprogressors). Chimerism data were confirmed by standard cytogenetics in two cases of donor–recipient sex mismatch. One patient (UPN 2957) did not have a marrow aspiration performed at day 30 and expired a few weeks later. Although strictly speaking not evaluable for engraftment, peripheral blood studies performed at day 20 revealed 80% donor chimerism. Of note, the HD patient with coexistent tMDS (UPN 3961) and a del(20q) abnormality had a fully diploid male (ie donor) karyotype at day 30. All of the long-term responders have ongoing 100% donor-derived engraftment which has lasted a minimum of 6 months.

Acute GVHD was diagnosed in 4/6 evaluable patients (Table 3). In UPN 3837, acute GVHD (grade 1) developed only after salvage chemotherapy and donor lymphocyte/stem cell infusion for treatment of disease progression. Chronic GVHD (Table 3) was present in 2/4 evaluable patients and was steroid responsive.

Regimen-related toxicity (RRT)

The RRT data are presented in Table 3. In keeping with the Bearman grading system,[10] viral pneumonia and intracerebral hemorrhage did not qualify as RRT. The patient who expired of intracerebral hemorrhage (UPN 3961) had coexistent therapy-related myelodysplasia. The maximal RRT experienced by the patients was grade 2. It was hepatic and gastrointestinal in most cases. Overall, the day 100 transplant-related mortality was 2/6 (33%), 1/4 (25%) in the sibling donor transplants.

Patient outcome and follow-up

As shown in Table 3, three patients have expired. Two expired on days 48 and 63, respectively, without any obvious evidence of disease progression. The other had progressive disease at day 100 restaging (UPN 3837). He received salvage chemotherapy followed by donor lymphocyte/stem cell infusions without response and eventually expired 8 months after the transplant. The other three patients are alive and progression-free, meeting CRU

Table 2 Stem cell source, engraftment and chimerism

UPN (Age/ Sex)	*Conditioning regimen*	*Donor type (sex)*	*Stem cell source*	*CD34⁺ cell dose (×10⁶/kg)*	*ANC 500 days*	*Platelet 20 K (days)*	*Cytogenetics day 30 (if sex mismatch present)*	*Chimerism day 30*	*Most recent chimerism*
2880 (29/M)	FC-ATG	Unrelated (female)	BM	3.8	11	19	100% diploid female	100% donor	100% donor (6 months)
2957 (29/M)	FC-ATG	Unrelated (male)	BM	3.6	12	0	NA	80% donor (day 20)	NA
3032 (22/M)	FM	Sibling (male)	PBSC	7.3	13	60	NA	100% donor	100% donor (26 months)
3588 (30/M)	FC-ATG	Sibling (male)	PBSC	4.3	13	0	NA	100% donor	100% donor (6 months)
3837 (29/M)	FC-ATG	Sibling (male)	PBSC	5.1	11	0	NA	75% donor	>95% donor (7 months)
3961 (30/F)	FLAG-IDA	Sibling (male)	PBSC	4.9	15	27	100% diploid male	100% donor	NA

UPN = Unique patient number; PBSC = peripheral blood stem cells; BM = bone marrow; FC-ATG = fludarabine–cyclophosphamide–antithymocyte globulin; FM = fludarabine–melphalan; FLAG-IDA = fludarabine–cytarabine–idarubicin; NA = not applicable.
See text for details on conditioning regimens.
ANC 500 is the first of 3 consecutive days of an absolute neutrophil count (ANC) of $\geqslant 500/\mu$l and platelet 20 K: the first of 7 consecutive days of an unsupported platelet count $\geqslant 20\,000/\mu$l. In three patients the platelet count never dropped below $20\,000/\mu$l after the conditioning regimen, hence the figure '0'.
UPN 2957 did not have a marrow aspiration performed at day 30. Peripheral blood studies at day 20, however, revealed 80% donor-derived chimerism.
UPN 3032 had his most recent chimerism study performed on peripheral blood. UPN 3837 achieved a >95% donor chimerism after salvage chemotherapy followed by a donor lymphocyte/stem cell infusion for treatment of disease progression.

Table 3 Regimen-related toxicity, GVHD and clinical outcome

UPN	*Donor type*	*Conditioning regimen*	*Maximal RRT grade*	*Acute GVHD*	*Chronic GVHD*	*Day 100 response*	*Current status*	*Latest follow-up (months after transplant)*	*Time and cause of death*
2880	Matched unrelated	FC-ATG	2	Yes (grade 2)	No	CRU	CRU	6 months)	
2957	Matched unrelated	FC-ATG	2	No	NA	NA	Expired	NA	Day 63: viral pneumonia
3032	Matched sibling	FM	1	Yes (grade 3)	Yes (extensive)	CRU (at 6 months)	CRU	26 months	
3588	Matched sibling	FC-ATG	2	No	Yes (limited)	CRU	CRU	9 months	
3837	Matched sibling	FC-ATG	2	Yes (grade 1)	No	PD	Expired	NA	8 months: progressive disease
3961	Matched sibling	FLAG-IDA	2	Yes (grade 3)	NA	NA	Expired	NA	Day 48: intracerebral hemorrhage

FC-ATG = fludarabine–cyclophosphamide–antithymocyte globulin; FM = fludarabine–melphalan; FLAG-IDA = Fludarabine–cytarabine–idarubicin; UPN = unique patient number; NA = not applicable; See text for details on conditioning regimens. GVHD = graft-versus-host disease (see text for grading); CRU = complete response, unconfirmed/uncertain; PD = progressive disease (see text for details on response definitions).
Regimen-related toxicity (RRT) graded according to Bearman *et al*.[10]

criteria with a median follow-up of 9 months (6–26). In all of them the remission accomplished by the allogeneic SCT has already exceeded in duration the one induced by the autologous procedure.

Discussion

The presence of a graft-versus-Hodgkin's effect following allogeneic SCT has been suggested by some, although not

all, published studies. Even if present, the high transplant-related mortality (50–60%) following allogeneic SCT in advanced HD would conceivably make its detection problematic. A recent report indicates that when patients are transplanted earlier during the course of their disease (ie in first or second relapse), such an effect can indeed be demonstrated, with a significantly lower relapse rate and an improved event-free survival in HD patients with chemosensitive disease when compared to autologous SCT.[14] These findings, as well as case reports of disease responses following donor lymphocyte infusions[15] support the existence of a graft-versus-Hodgkin's effect.

Allogeneic SCT following less intensive or non-myeloablative conditioning regimens is yielding very promising early results in several hematologic malignancies, presumably due to its ability to harness a graft-versus-leukemia or lymphoma effect within the contest of a reduced transplant-related toxicity.[7,8] Heavily pretreated patients with advanced HD may be good candidates for this approach, as their ability to tolerate conventional myeloablative preparative regimens is limited. Indeed, preliminary results have suggested that non-myeloablative conditioning may indeed be feasible in these patients, albeit within the context of a double autologous/allogeneic SCT approach.[16]

The main purpose of this study was to explore the feasibility of fludarabine-based conditioning for allografting in advanced HD. The regimen proved to be well tolerated, with manageable and non-fatal regimen-related toxicity even in these heavily pretreated patients that had recently recurred after a myeloablative autologous SCT. This in keeping with recent reports employing similar regimens in the setting of leukemia and lymphoma.[17–19]

Half (3/6) of these patients are alive and progression-free with a median follow-up of 9 months. The agents included in the preparative regimens employed, at the doses described, would be expected to produce only transient responses at best in these high-risk, heavily pretreated patients. Yet all of these responses have already outlived the ones induced by the autologous SCT. Although unproven, it is not unreasonable to speculate that an immunological effect of the infused stem cells (ie a graft-versus-Hodgkin's effect or 'adoptive immunotherapy') may indeed play a significant role in these responses, whose durability remains to be determined. Interestingly, all three responders had evidence of acute and/or chronic GVHD.

In the absence of persistent disease, a reduced-intensity, fludarabine-based preparative regimen consistently allowed early (ie day 30) and complete engraftment of allogeneic PBSC from matched sibling donors. Engraftment of matched unrelated donor marrow was documented in at least one patient, with another patient showing early (ie day 20) high-grade (ie 80%) peripheral blood donor-derived chimerism. This is probably related to the underlying immunosuppression of these patients, due to their disease and its treatment. The ability to employ unrelated donors, if confirmed in a larger number of cases, could substantially expand the number of patients eligible for this treatment. Complete donor-derived engraftment has proved long lasting (ie at least 6 months) so far.

The target antigens for a possible graft-versus-Hodgkin's effect are unknown. Overall, up to 40–50% of HD in Caucasians is reported to be EBV associated, and EBV antigens could be involved. The incidence of EBV positivity in the nodular sclerosis variant (two-thirds of patients in this study) is only 10–30%,[20] and all three patients for whom EBV testing was performed proved to be negative. The paucity of the data does not allow, however, for any meaningful correlation between EBV status and response.

In conclusion, allogeneic stem cell transplantation with reduced-intensity, fludarabine-based conditioning is feasible in very high-risk, heavily pretreated HD patients, with acceptable engraftment and regimen-related toxicity, as well as encouraging preliminary results. This approach seems well tolerated and deserves to be explored further in a larger number of patients. Longer follow-up data will be required to assess the ultimate impact on patient outcome.

Note

In March 2000, we were notified that one patient (UPN 2880) had expired on 8 November 1999 (8 months after his transplant). Based on verbal reports the cause of death was Nocardia pneumonia. According to a preliminary autopsy report, he had no evidence of active HD at post-mortem exam. Another patient (UPN 3032) remains in remission from his HD (31 months after his transplant). He was treated successfully for several infectious complications, including systemic aspergillosis, Nocardia pneumonia and CMV infection. He has no active chronic GVHD and is off all medications (including immunosuppressant drugs). Lastly, the third patient (UPN 3588) had an asymptomatic, smoldering, biopsy-proven thoracic recurrence of his HD (right hilar area) diagnosed in February 2000 (15 months after his transplant). He has since received a donor lymphocyte/stem cell infusion, which was not preceded by salvage chemotherapy.

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References

1 Urba WJ, Longo DL. Hodgkin's disease. *New Engl J Med* 1992; **326**: 678–687.
2 Aisenberg AC. Problems in Hodgkin's disease management. *Blood* 1999; **93**: 761–779.
3 Forman SJ. Role of high-dose therapy and stem cell transplantation in the management of Hodgkin's disease. *American Society of Clinical Oncology Educational Book*, Alexandria, VA, 1997, pp 244–247.
4 Gajewski JL, Phillips GL, Sobocinski KA *et al*. Bone marrow transplants from HLA-identical siblings in advanced Hodgkin's disease. *J Clin Oncol* 1996; **14**: 572–578.
5 Milpied N, Fielding AK, Pearce R *et al*, for the European Group for Blood and Marrow Transplantation. Allogeneic bone marrow transplant is not better than autologous transplant for patients with relapsed Hodgkin's disease. *J Clin Oncol* 1996; **14**: 1291–1296.
6 Anderson JE, Litzow MR, Appelbaum FR *et al*. Allogeneic,

syngeneic and autologous marrow transplantation for Hodgkin's disease: the 21-year Seattle experience. *J Clin Oncol* 1993; **11**: 2342–2350.
7 Martino R, Sierra J. Allogeneic hematopoietic stem cell transplantation after immunosuppressive but non-myeloablative conditioning: 'miniallografts' are no small matter. *Haematologica* 1998; **83**: 865–867.
8 Champlin R, Khouri I, Kornblau S *et al*. Allogeneic hematopoietic transplantation as adoptive immunotherapy: induction of graft-vs.-malignancy as primary therapy. *Hematol/Oncol Clin N Am* 1999; **13**: 1041–1057.
9 Yam P, Petz L, Knowlton R *et al*. Use of DNA restriction fragment length polymorphism to document marrow engraftment and mixed hematopoietic chimerism following bone marrow transplantation. *Transplantation* 1987; **43**: 399–405.
10 Bearman SI, Appelbaum FR, Buckner CD *et al*. Regimen-related toxicities in patients undergoing bone marrow transplantation. *J Clin Oncol* 1988; **6**: 1562–1568.
11 Glucksberg H, Storb R, Fefer A *et al*. Clinical manifestations of graft versus host disease in human recipients of marrow from HLA matched sibling donors. *Transplantation* 1974; **18**: 295–304.
12 Schulman HM, Sullivan KM, Weiden PL *et al*. Chronic graft-versus-host disease syndrome in man. A long term clinical pathological study of 20 Seattle patients. *Am J Med* 1980; **69**: 204–212.
13 Pallesen G, Hamilton-Dutoit SJ, Rowe M, Young LS. Expression of Epstein–Barr virus latent gene products in tumor cells of Hodgkin's disease. *Lancet* 1991; **337**: 320–322.
14 Akpek G, Ambinder RF, Piantadosi S *et al*. Long-term follow-up of bone marrow transplantation for Hodgkin's disease: evidence for a graft-versus-tumor effect. *Proc Am Soc Clin Oncol* 1999; **18**: 53a (Abstr.).
15 Porter DL, Connors JM, Van Deerlin VMD *et al*. Graft-versus-tumor induction with donor leukocyte infusion as primary therapy for patients with malignancies. *J Clin Oncol* 1999; **17**: 1234–1243.
16 Carella AM, Lerma E, Dejana A *et al*. Autografting followed by mini-allografting in hematologic neoplasia and breast cancer. *Bone Marrow Transplant* 1999; **23** (Suppl. 21): (Abstr.).
17 Giralt S, Estey E, Albitar M *et al*. Engraftment of allogeneic hematopoietic progenitor cells with purine analog-containing chemotherapy: harnessing graft-versus-leukemia without myeloablative chemotherapy. *Blood* 1997; **89**: 4531–4536.
18 Slavin S, Nagler A, Naparstek E *et al*. Nonmyeloablative 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 disease. *Blood* 1998; **91**: 756–763.
19 Khouri I, Keating M, Körbling M *et al*. Transplant-lite: induction of graft-versus-malignancy using fludarabine-based nonablative chemotherapy and allogeneic blood progenitor-cell transplantation as treatment for lymphoid malignancies. *J Clin Oncol* 1998; **16**: 2817–2824.
20 Chapman ALN, Rickinson AB. Epstein–Barr virus in Hodgkin's disease. *Ann Oncol* 1998; **9** (Suppl. 5): (Abstr. S5–S16).