Clinical evidence of a graft-versus-Hodgkin’s-lymphoma effect after reduced-intensity allogeneic transplantation

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Summary

Background In patients with multiply relapsed Hodgkin’s lymphoma, the use of allogeneic stem-cell transplantation has been limited by prohibitive non-relapse-related mortality rates and by a lack of definitive evidence for a therapeutic graft-versus-tumour effect. Therefore, we aimed to assess the graft-versus-tumour effect of reduced-intensity allogeneic transplantation.

Methods We undertook reduced-intensity transplantation in 49 patients with multiply relapsed Hodgkin’s lymphoma, 44 (90%) of whom had progression of disease after previous autologous transplantation (median age 32 years [range 18–51], number of previous treatment courses was five [range 3–8], and time from diagnosis 4.8 years [range 0.6–4.8]). 31 patients had HLA-matched donors who were related and 18 had donors who were unrelated. Median follow-up was 967 days (range 102–2232). The primary endpoints were engraftment, toxic effects, non-relapse-related mortality, incidence of graft-versus-host disease (GVHD), and the toxic effects of adjuvant donor-lymphocyte infusion.

Findings All patients engrafted. Eight of 49 (16%) had grade II–IV acute GVHD and seven (14%) had chronic GVHD before donor-lymphocyte infusion. 16 (33%) patients received donor-lymphocyte infusion from 3 months after transplantation for residual disease or progression. Six (38%) of the 16 developed grade II–IV acute GVHD and five developed chronic GVHD. Nine (56%) showed disease responses after infusion (eight complete, one partial). Non-relapse-related mortality was 16·3% at 730 days (7·2% for patients who had related donors vs 34·1% for those with unrelated donors, p=0.0206). Projected 4-year overall and progression-free survival were 55·7% and 39·0%, respectively (62·0% and 41·5% for related donors).

Interpretation These data show the potential for durable responses in patients who have previously had substantial treatment for Hodgkin’s lymphoma. The low non-relapse-related mortality suggests the procedure could be undertaken earlier in the course of the disease.

Introduction

Hodgkin’s lymphoma is one of the haematological malignant diseases that is most responsive to chemotherapy. However, few patients with multiply relapsed or refractory disease will be cured by conventional chemotherapy. Myeloablative doses of chemotherapy, with the use of autologous stem cells, can lead to durable responses in 40–50% of patients with multiply relapsed disease and in 25–40% of refractory patients, but those who relapse after these procedures have only a restricted range of therapeutic options that might offer cure.

Interest in the use of allogeneic haemopoietic stem-cell transplantation derives not only from the cytoreductive effect caused by high doses of chemoradiotherapy, but also from the potential benefit of an immune-mediated graft-versus-tumour effect. This benefit was initially suggested in chronic myeloid leukemia by the decreased relapse rates in patients who developed graft-versus-host disease (GVHD) and by the raised rates of relapse in those receiving T-cell-depleted grafts or syngeneic grafts. Moreover, infusions of donor lymphocytes have reinuced remissions in 60–80% of patients with chronic myeloid leukemia who relapsed in the chronic phase. The use of allogeneic therapies for patients with Hodgkin’s lymphoma has historically been restricted by non-relapse-related mortality rates of 43–61%. Thus, allogeneic haemopoietic stem-cell transplantation has not shown any survival advantage over autologous stem-cell transplantation in matched patient cohorts. Furthermore, evidence for a strong graft-versus-lymphoma effect in patients with Hodgkin’s lymphoma is sparse.

Several studies have suggested lower relapse rates for allogeneic transplantation than those for autologous transplantation, although interpretation of the findings is hindered by small numbers of patients, by high non-relapse-related mortality in the allogeneic group, and by differences in baseline characteristics of patients and in conditioning therapies between groups. Some workers have investigated the use of donor-lymphocyte infusion in patients who had relapsed after allogeneic transplantation. In many cases, the responses were of short duration, or it had been difficult to differentiate between the contribution of preceding chemotherapy and that of donor-lymphocyte infusion to the development of responses.

Our aim was to assess the potential of allogeneic transplantation in patients with Hodgkin’s lymphoma by use of reduced-intensity transplantation and through...
T-cell depletion of both the recipient and the graft to keep to a minimum the risk of GVHD and thus diminish non-relapse-related mortality.

Methods

Patients

Patients were eligible for study entry if they had multiply relapsed Hodgkin’s lymphoma and had had autologous stem-cell transplantation (or if they were for some reason excluded from doing so). Patients who had a left ventricular ejection fraction of less than 40%, creatinine clearance of less than 40 mL per min, bilirubin of greater than 34 µM/L, or liver transaminases more than three times the upper normal limit were excluded from the study.

Study design

The study protocol was approved by the local institutional ethics committees. Patients and donors gave written informed consent. The conditioning regimen for transplantation consisted of: 30 mg/m² per day intravenous fludarabine from day 7 before transplantation to day 3 before transplantation (ie, five doses); 140 mg/m² melphalan on day 2 before transplantation; and intravenous alemtuzumab (a monoclonal antibody against CD52). 36 patients received 100 mg intravenous alemtuzumab given as 20 mg per day from day 8 to day 4 before transplantation. De-escalation of the alemtuzumab dose was subsequently introduced to diminish the delay in immune reconstitution, and to thus enhance graft-versus-tumour activity and restrict infection-related deaths.16 13 patients were given lower doses intravenously: 90 mg (3×30 mg; n=1) from day 8 to day 6, 60 mg (2×30 mg; n=9) from day 8 to day 7 or day 3 to day 2, and 50 mg (5×10 mg; n=3) from day 5 to day 1. 3 mg/kg per day intravenous ciclosporine was first given on the day before transplantation as further prophylaxis against GVHD. On the day of transplantation, patients received unmanipulated allogeneic peripheral-blood stem-cell grafts mobilised with granulocyte colony-stimulating factor from their HLA-matched related donor (n=31) or unrelated donor (n=6), or received unmanipulated bone-marrow grafts (most patients with an unrelated donor, n=12).

Patients were screened for cytomegalovirus infection by PCR detection of viral DNA or by the viral pp65 antigenaemia assay. Pre-emptive intravenous ganciclovir or foscarnet was given according to institutional guidelines. Fungal infections were classified as proven, probable, or possible according to guidelines defined by the European Organisation for Research and Treatment of Cancer Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG).17 In the absence of GVHD, ciclosporine was reduced from 3 months after transplantation. Disease restaging was done every 3 months after transplantation until 1 year. Chimerism analyses were assessed at similar time points in those eligible for intervention (ie, those without GVHD). Subsequent frequency of testing depended on previous results and on the need for therapeutic intervention (every 3 months in those receiving interventions and every 6 months or as needed for clinical signs of relapse in other patients).

Those with progressive disease were eligible for donor-lymphocyte infusion in the absence of GVHD. Escalating doses of CD3-positive lymphocytes were given every 3 months in the absence of development of GVHD if there was no evidence of disease response. Patients with persistent mixed chimerism were also eligible for donor-lymphocyte infusion because this state might represent lymphohaemopoietic tolerance and could be a marker of increased relapse risk. Chimerism was assessed by PCR analysis of informative minisatellite regions (ie, short tandem-repeat loci).

All patients receiving donor-lymphocyte infusion who had diagnostic tumour blocks available underwent screening for infection of Reed-Sternberg cells by Epstein-Barr virus by in-situ hybridisation for virus-encoded small RNA (EBER) transcripts and for expression of viral latent membrane protein.

The primary endpoints of the study were to assess engraftment, toxic effects, non-relapse-related mortality, incidence of GVHD, and the toxic effects of adjuvant donor-lymphocyte infusion. Acute GVHD was assessed according to the International Bone Marrow Transplant Registry criteria; acute and chronic GVHD after donor-lymphocyte infusion were graded according to consensus criteria.18 The main secondary endpoint was disease response, which was assessed by radiological imaging—CT, positron-emission tomography (PET), or combined modality imaging (CT-PET). The technique used for restaging depended on local policy and availability. Responses were defined by standard volume criteria in those staged by CT and defined as: complete remission (no evidence of Hodgkin’s lymphoma); unconfirmed complete remission (patient fulfilled criteria for complete remission but had a residual lymph-node mass >1.5 cm in diameter that regressed by more than 50% after chemotherapy); partial remission (substantial reduction of all lesions and decrease of large lymph nodes or measurable organ lesions by >50% at the largest diameter, for mediastinal involvement reduction of the tumour by >25% in the maximum thoracic diameter); or refractory (if the above criteria were not met). In those who underwent functional imaging, complete remission was defined as the absence of nodal or parenchymal lesions that were avid for 18-fluorodeoxyglucose ([18F]FDG).

Statistical analysis

Data were analysed according to previously published guidelines for assessment of outcomes after trans-
Time-to-event outcomes with competing risks (ie, non-relapse-related mortality, relapse incidence, and GVHD) were estimated as cumulative-incidence curves. Non-relapse-related mortality was defined as the date of transplantation until death from causes other than relapse, and relapse was defined as a competitive risk in analysis of non-relapse-related mortality. Non-relapse-related mortality was defined as a competitive risk in analysis of relapse incidence, and death without GVHD as a competitive risk in GVHD analysis. Comparison of cumulative-incidence curves in univariate analyses was done by Lunn and McNeill's approach, in which Cox regression is applied to competing risks. Actuarial curves were estimated for overall survival, progression-free survival (measured from transplantation until progression or death from any cause), and current progression-free survival according to the Kaplan-Meier method. Patients who responded to donor-lymphocyte infusion without subsequent progression at the time of analysis were censored at the last follow-up date in the analysis of current progression-free survival. The log rank test was used to compare survival curves for different subgroups on univariate analyses. Any p values less than or equal to 0.05 were defined as significant.

Role of the funding source
The sponsors of the study had no involvement in study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication. The corresponding author had full access to all the data and had final responsibility to submit the article for publication.

Results
49 patients were enrolled between Oct 3, 1997, and Aug 21, 2003, from seven centres in the UK. Table 1 shows baseline characteristics of patients. Median follow-up of those alive (n=31) was 967 days (range 102–2232).

The median CD34+ cell dose (which shows a threshold effect for engraftment potential) was 4.8×10^6 per kg (range 1.3–19.2). All 49 patients achieved sustained engraftment. Median time to a neutrophil count greater than 0.5×10^9 per L was 12 days (8–35), and median time to an unsupported platelet count greater than 20×10^9 per L was 12 days (3–99, three patients did not reach this count at time of death). Informative chimerism analyses

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<tr>
<td>Women</td>
<td>24 (49%)</td>
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<tr>
<td>Matched related</td>
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<td>Matched unrelated</td>
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<td>Number who had previous autograft</td>
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<tr>
<td>Time from autograft to allograft (years)</td>
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<td>Complete response or complete response uncertain</td>
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<tr>
<td>Partial response</td>
<td>25 (51%)</td>
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<tr>
<td>Refractory</td>
<td>15 (31%)</td>
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<td>1 (2%)</td>
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<td>100 mg</td>
<td>36 (73%)</td>
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<tr>
<td>&lt;100 mg</td>
<td>13 (27%)</td>
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</table>

Data are number of individuals (%) or median (range).

Table 1: Baseline characteristics

Figure 1: Cumulative-incidence curves according to donor type
A=non-relapse-related mortality. B=acute grade II–IV GVHD. C=chronic GVHD. B and C curves include GVHD after donor-lymphocyte infusion.
were available for 30 patients 3 months after transplantation; 24 (80%) were full donor chimeras and six (20%) were mixed chimeras (80–95% donor). Of the full donor chimeras, 17 remained full donor at 6 months, two were mixed in the T-cell lineage, three were not evaluable, and repeat analyses were not done for two. Of those with mixed chimerism at 3 months, only one was full donor by 6 months. Chimerism analyses for three further patients at 6 months after transplantation showed that all were mixed chimeras (>80% donor).

After transplantation, eight of 49 (16%) patients developed acute grade II–IV GVHD (six grade II and two grade III) before donor-lymphocyte infusion. Ten of 49 (20%) patients developed grade I cutaneous acute GVHD after transplantation but before donor-lymphocyte infusion. Seven patients developed chronic GVHD (four limited and three extensive), which occurred de novo in four patients and after acute GVHD in three.

15 (88%) of 17 patients at high risk of infection with cytomegalovirus (ie, seropositive recipients) and four (44%) of nine intermediate-risk patients (ie, seronegative recipient and seropositive donor) developed cytomegalovirus infection; two patients developed cytomegalovirus disease. Two of 49 (4%) patients acquired adenovirus disease (one systemic and one gastrointestinal). Other viral infections were also common: respiratory syncytial virus (n=4), parainfluenza (n=4), influenza A (n=2), and reactivation of varicella zoster (n=10). Proven or probable invasive pulmonary aspergillosis occurred in five patients.

Other toxic effects on organs were uncommon and none were fatal. One patient developed interstitial pneumonitis of unknown cause, one had a cardiomyopathy, and one had two episodes of haematemesis that were managed conservatively. One patient developed thrombotic thrombocytopenic purpura, one had secondary acute myeloid leukaemia, and one had asptic bone necrosis.

Five (10%) patients died from early complications of transplantation (two from cytomegalo virus disease, one from systemic adenovirus infection, one from thrombotic thrombocytopenia purpura, and one bacterial pneumonia).

Cumulative incidence of non-relapse-related mortality was 4·1% (95% CI 1·1–15·9) at 100 days after transplantation and 16·3% (8·2–32·3%) at 730 days. Non-relapse-related mortality was significantly higher in those with unrelated donors than in those with related donors at 730 days (34·1% [16·5–70·3] vs 7·2% [1·9–27·5], p=0·0206, figure 1). Relapse or progression occurred in 21 (43%) patients.

19 (39%) patients received donor-lymphocyte infusion, 16 for progressive disease (three of whom had further cytoreductive chemotherapy before donor-lymphocyte infusion) and three for mixed chimerism (table 2). 13 patients developed GVHD (12 of whom were treated for progression and one for mixed chimerism), with acute presentation in eight patients (one grade I, two grade II, three grade III, and two grade IV) and chronic presentation in five (two limited, three extensive). Overall cumulative incidence of acute grade II–IV GVHD including before and after donor-lymphocyte infusion was 21·0% (95% CI 12·1–36·5) at 365 days and 32·6% (20·9–50·7%) at 730 days. Cumulative incidence of acute grade II–IV GVHD before and after donor-lymphocyte infusion was 16·5% (7·4–36·8) at 365 days and 24·9%
(13.0–47.9%) at 730 days for recipients with related donors, and 28.2% (13.4–59.5) at 365 days and 49.7% (27.8–88.6) at 730 days for the group who had unrelated donors (figure 1).

At 730 days, cumulative incidence of chronic GVHD was 22.6% (13.1–39.1%) overall, 17.7% (8.0–39.2%) in the group who had related donors, and 39.1% (20.9–73.5%) in recipients with unrelated donors (figure 1). The excess GVHD in the unrelated group was not significant for either acute or chronic GVHD. Two evaluable patients who were treated for mixed chimerism converted to full-donor status in the absence of GVHD. Nine (56%) of 16 patients treated for progression had a response (eight complete and one partial), seven of whom had not received chemotherapy before donor-lymphocyte infusion (table 2). Two patients treated for progression and one treated for mixed chimerism died from GVHD and its treatment; both of those who had disease progression attained a complete response before death. Two patients who responded subsequently progressed (at 427 days and 827 days after donor-lymphocyte infusion, respectively), and five patients who did not receive chemotherapy before infusion had complete responses at a median of 675 days (range 296–1038) after the last dose of donor-lymphocyte infusion (table 2).

Histological samples were available for analysis of the presence of Epstein-Barr virus in tumour samples of 11 patients receiving donor-lymphocyte infusion, eight of whom had infusion for disease progression. Results of in-situ hybridisation for EBER (Epstein-Barr-virus-encoded RNA) transcripts showed that seven patients were negative and one was positive, consistent with the age and histological subtype of the patients (seven nodular sclerosing, one mixed cellularity). Five of the seven patients who were EBER-negative had disease responses, as did the patient who was EBER-positive. 14 (67%) of the 21 patients who relapsed had no previous history of GVHD, and a further five (24%) had clinically mild grade I acute or limited chronic GVHD that had been effectively treated with topical steroids (figure 2). Nine (56%) of the 16 patients who received donor-lymphocyte infusion had clinically substantial (ie, grade II–IV acute or extensive chronic) GVHD, seven of whom achieved a complete response, compared with one of seven patients without such GVHD (figure 2). Thus, achievement of complete response after donor-
lymphocyte infusion was significantly associated with the development of grade I–IV acute GVHD or extensive chronic GVHD (p=0.0148). 18 (37%) patients died during the study, and 31 (63%) were censored as alive in the statistical analysis of overall survival at the latest follow-up (Nov 13, 2003). Actuarial 4-year overall survival was 55·7% (95% CI 39·3–72·0), and was 62·0% (42·3–81·6) for patients with related donors compared with 45·1% (18·3–71·8) for those with unrelated donors (p=0·0389, figure 4). 4-year progression-free survival was 32·4% (16·5–48·3%) for those with related donors compared with 45·1% (18·3–71·8) for those with unrelated donors (p=0·0389, figure 3). 4-year overall survival was 39·0% (22·8–55·1), and was 41·5% (21·7–61·3) for those with related donors compared with 33·9% (5·9–62·0) for the group with unrelated donors (p=0·4202, figure 4).

Disease status at transplantation (ie, complete responders [n=8] versus partial response [n=25] or refractory disease [n=15]) had a significant effect on overall survival (100% vs 51·4% [95% CI 24·8–78·0] for partial response and 35·9% [10·2–61·6] for refractory disease, p=0·0398) and on current progression-free survival (83·3% [52·9–100] vs 33·6% [9·6–57·5] for partial response and 21·8% [0–44·0] for refractory disease, p=0·0389) in univariate analysis (figure 4), with a trend towards improved progression-free survival (66·7% [28·2–100] vs 25·2% [95% CI 2·0–48·3%] for partial responders and 21·8% [0–44·0%] for refractory disease, p=0·1070). However, no significant differences were recorded between individuals with partial response and those with refractory disease. Alemtuzumab dose and stem-cell source had no effect with univariate analyses. Previous autograft significantly affected progression-free survival (23·7% [7·2–40·2] vs 80·0% [44·2–100]) for those without, p=0·0267 but not overall survival (52·4% [34·5–70·3] vs 80·0% [44·2–100], p=0·2454).

**Discussion**

Our study of patients receiving reduced-intensity allogeneic haemopoietic stem-cell transplantation either from related or unrelated donors has shown potential benefit in terms of durable response.

Clinical outcomes for patients with relapsed or refractory Hodgkin’s lymphoma who have had autologous transplantation have seemed better than for those who had allogeneic haemopoietic stem-cell transplantation, leading many physicians to believe that autologous transplantation is the current standard of care for patients who are beyond remission or who have primary refractory disease. Previous autologous haemopoietic stem-cell transplantation is a risk factor for non-relapse-related mortality after allogeneic transplantation, and has been associated with non-relapse-related mortality rates of 48–61% in patients with Hodgkin’s lymphoma. Most patients in these studies had sibling donors. In our study, the non-relapse-related mortality of 16·3% at 730 days suggests that reduced-intensity allogeneic transplantation leads to fewer toxic effects than do conventional transplantation protocols that use more intensive conditioning. However, a randomised study would be needed to exclude selection bias. In the cohort who had related donors, non-relapse-related mortality was 7·2%. The rates of non-relapse-related mortality in our study compare favourably with those of a large single-centre study of patients with matched sibling donors who underwent allogeneic transplantation as the initial transplant modality (non-relapse-related mortality, 43%).

Although our use of the reduced-intensity allograft protocol achieved durable engraftment with a fairly low incidence of severe GVHD (grade III–IV) and comparatively low non-relapse-related mortality, translation into improved survival might be compromised by both the reduced antitumour activity of the conditioning therapy and the delayed reconstitution of immunity that results from T-cell-depletion strategies. 140 mg/m2 melphalan has moderate antitumour activity, but most patients had relapsed after an autograft conditioned with Carmustine, etoposide, cytarabine, and...
Fludarabine has only modest activity in Hodgkin’s lymphoma.\(^5\) and Hodgkin and Reed-Sternberg cells are not direct targets for alemtuzumab-mediated lysis because they do not express CD52 antigen.\(^6\) An indirect effect might be present, mediated by activity against cytokine-secreting accessory cells that express CD52 and which are abundant in Hodgkin’s lymphoma. However, the agents included in the preparative regimen would be expected to produce only transient responses at best in these high-risk patients. Thus, although these agents are important in maintaining tumour control until immune reconstitution, the long-term durability of responses probably relies on an immunological effect of the infused cells.

Effective restoration of antitumour immunity with donor lymphocytes after resolution of tissue damage and cytokine release caused at the time of transplantation (which potentiate the priming of harmful graft-versus-host alloreactivity) relies on the existence of a therapeutically relevant graft-versus-lymphoma effect. Our data show that immune reactivity can mediate durable antitumour responses. Consistent with many other studies of malignant disease responsive to donor-lymphocyte infusion, GVHD after infusion seemed to be associated with antitumour response. This finding suggests that the immunological targets of the effectors of these responses are allogeneic rather than tumour-specific (eg, minor histocompatibility antigens that have widespread tissue distribution). However, other tumour-specific effectors such as viral peptides expressed by tumour cell might be targets. For example, Epstein-Barr virus RNA can be localised to Hodgkin and Reed Sternberg cells in 20–40% of patients with Hodgkin’s lymphoma (especially those with mixed cellularity). Our data do not exclude the possible role of antiviral effectors to Hodgkin’s lymphoma responses, but most patients who responded to donor-lymphocyte infusion had EBER-negative tumours.

Low non-relapse-related mortality combined with responses to donor-lymphocyte infusion in some patients who had previously relapsed is an encouraging finding. Comparison of our study with other series is difficult, although overall survival (62.0% at 4 years) and current progression-free survival (41.5% at 4 years) in the group with related donors compares favourably with that of registry data for 100 matched-sibling allograft recipients who underwent conventional conditioning (overall survival 21% [14.0–30.0] at 3 years),\(^2\) and 53 patients who underwent matched-sibling allogeneic transplantation as the first transplant modality (overall survival 30% [18.0–41.0] at 5 years, progression-free survival 27% [21.0–34.0] at 5 years).\(^3\) However, fewer patients (25 [47%]) in the study of 53 patients were chemosensitive at time of transplantation than in our series (33 patients). Data for reduced-intensity approaches in Hodgkin’s lymphoma is limited. Sustained responses have been recorded in three small studies of patients with Hodgkin’s lymphoma after reduced intensity transplantation (13 of 29 patients in total),\(^4,5,26\) but median follow-up was less than 12 months in two of these studies.\(^2,26\)

The importance of our results for directing future clinical practice is difficult to define. Improved outcome after induction treatment with the latest generation of chemotherapy implies that patients who are refractory or relapsing represent a cohort whose outlook is becoming more unfavourable as results for patients with primary disease improve. The patients in our study had been treated with modern salvage regimens but few had attained a complete response before transplantation. Furthermore, they had previously received more lines of chemotherapy and were further from diagnosis than were the patients in most series of autologous transplantation. Indeed, most of those in our study previously underwent autologous transplantation and had subsequently relapsed. Comparison with groups in previous studies is therefore restricted and there is no appropriate cohort with whom to do a case-control analysis. Moreover, some patients in our study may continue to be chemosensitive but yet have recurrent relapses (ie, have chronic relapsing Hodgkin’s lymphoma) and could be selected as a group with unusual disease biology, generally with slow disease progression. This group may have a better outlook after high-dose therapy than would a less highly selected group of patients with early disease.\(^2,27\)

The introduction of new functional-imaging modalities such as \([^{18}F]\)FDG-PET can affect disease staging, leading to the upstaging of patients with few residual masses on CT scanning and to downstaging of those with large residual masses that are not FDG-avid.\(^28\) Previous studies have defined response criteria based on conventional radiographic characteristics, recognising that CT cannot differentiate between viable tumour and fibrotic tissue. Theoretically, functional imaging will improve outcomes in low-risk (ie, chemosensitive or complete-response) groups by excluding patients with residual small-volume viable tumour and will worsen outcomes in high-risk groups (ie, those with a large residual mass or those that have not shown complete response) by excluding those with residual fibrotic masses but no viable tumour. \([^{18}F]\)FDG-PET before transplantation in patients who have responded to salvage chemotherapy has both a high positive predictive value and a negative predictive value for disease progression after autologous transplantation.\(^29\) Such approaches may thus identify patients who might be suitable for early allogeneic transplantation.

However, these data are preliminary and need confirmation before use in transplantation strategies. Most patients in our study were classified as having achieved a partial response before transplantation on the basis of conventional radiographic criteria. Functional
imaging was not routinely done before transplantation, but further assessment of its prognostic importance in this cohort is clearly warranted. Other prognostic indicators of poor outcome after autologous transplantation, such as short duration of response to initial chemotherapy, could also help identify groups who might benefit from early allogeneic transplantation.

We conclude that our data are evidence for a clinically relevant graft-versus-Hodgkin’s-lymphoma effect and, combined with low non-relapse-related mortality, provide a rationale for reassessment of the role of allogeneic transplantation in the management of Hodgkin’s lymphoma.

Contributors
K S Peggs collated the data from individual centres, did the data analysis, and wrote the article. All authors were responsible for the implementation of the study, management of patients, and data collection at the study sites and had the opportunity to comment on the report. A Dogan was responsible for the histological assessment of Epstein-Barr virus status.

Conflict of interest statement
We declare that we have no conflict of interest.

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We declare that we have no conflict of interest.

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