

The role of allogeneic transplantation in non-Hodgkin's lymphoma

Karl S. Peggs, Stephen Mackinnon and David C. Linch

Department of Haematology, Royal Free and University College London Medical Schools, London, UK

Summary

The evolution of combination chemotherapy regimens, combined with improvements in supportive care, has incrementally improved survival outcomes for patients with non-Hodgkin's lymphomas (NHL). Although 40–60% of younger patients with diffuse large cell lymphoma can now expect to be cured, significant numbers will either fail to achieve a remission or relapse after attaining a remission. In addition, certain histological subtypes are associated with particularly poor prognoses with combination chemotherapy alone (e.g. mantle cell lymphoma, B-cell prolymphocytic leukaemia). Relatively few of these patients can achieve long-term responses. Other NHL subtypes, whilst associated with more favourable prognoses in terms of overall survival, are rarely, if ever, cured (e.g. most low grade NHL including follicular lymphoma, chronic lymphocytic leukaemia and small lymphocytic lymphoma). For these reasons dose escalation and allogeneic transplantation have been investigated as potential ways of improving outcome, although this has mainly been in the setting of advanced disease. Any possible benefits have frequently been out-weighted by procedural morbidity and mortality. The parallel development of transplantation approaches that limit procedural toxicity along with advances in supportive care require that the role of allogeneic haematopoietic stem cell transplantation in the management of lymphoma be re-evaluated.

Keywords: non-Hodgkin lymphoma, allogeneic transplantation, donor lymphocyte infusion, reduced intensity, immunotherapy.

Rationale for allogeneic transplantation

The central themes that form the rationale behind the development and application of allogeneic transplantation approaches are that:

- 1 Tumours show a dose–response relationship to chemotherapy and that the escalation of the latter is limited by collateral organ damage, in particular by toxicity to the stem cell compartment.
- 2 An allogeneic stem cell source provides a pluripotent progenitor pool that is free of tumour contamination.
- 3 Donor-derived immune cells are potentially capable of mediating graft-*versus*-tumour (GvT) effects, either specifically or as part of an alloreactive phenomenon.

Proof of principle for the first of these is provided for a number of lymphomas by the success of high dose therapies with autologous stem cell rescue. These approaches allow successful long-term salvage of 40–50% of selected patients with relapsed diffuse large B-cell lymphoma (DLBCL). As long as procedure-related mortality can be kept low, reduced relapse rates can be translated into better overall (OS) and disease-free survival (DFS) rates compared with conventional chemotherapy, as demonstrated in a number of prospective randomized studies (Philip *et al*, 1995; Schouten *et al*, 2003). A common finding from these studies is that results are better in those patients whose disease remains chemo-sensitive prior to autologous transplantation. The benefits in chemo-refractory cases, particularly with modern induction and salvage therapies, are minimal and any prolongation of disease control is usually offset by procedural toxicity. Thus disease status and chemo-sensitivity at the time of transplantation are important factors to consider when evaluating allogeneic transplantation series.

Evidence that provision of a stem cell source that is free from tumour contamination may also contribute to outcome by reducing disease relapse comes from a number of sources. Studies incorporating purging strategies that aim to reduce or eliminate tumour contamination of autologous grafts have given contradictory results (Williams *et al*, 1996; Freedman *et al*, 1999; van Besien *et al*, 2003; Schouten *et al*, 2003). A recent analysis of patients receiving syngeneic grafts led to the suggestion that the major component of any benefit conferred by allografting results directly from the lack of tumour contamination of these grafts (Bierman *et al*, 2003). The reduced risk of relapse in allogeneic compared with autologous transplant recipients, as detailed in many other studies and often equated with a graft-*versus*-malignancy effect

Correspondence: Department of Haematology, Royal Free and University College London Medical Schools, 98 Chenes Mews, London WC1E 6HX, UK. E-mail: kpeggs@hotmail.com

(Jones *et al*, 1991; Ratanatharathorn *et al*, 1994; Schimmer *et al*, 2000; Peniket *et al*, 2003), was confirmed. However, no significant differences in relapse rates were observed when results of allogeneic transplantation ($n = 893$) were compared with syngeneic transplantation ($n = 89$) for any histological subtype of non-Hodgkin's lymphoma (NHL), and T-cell depletion (TCD) of allografts was not associated with a higher risk of relapse. The analyses also failed to show a lower relapse rate in patients who developed graft-*versus*-host disease (GvHD). All of these factors have historically been acknowledged as indirect surrogate markers for potential graft-*versus*-malignancy activity, as first suggested for chronic myeloid leukaemia. Interpretation is complicated by the heterogeneity in disease histology and lack of information on other characteristics that might influence transplant outcomes, such as disease chemo-sensitivity (unknown or untested in >50% of allograft recipients). Inclusion of more poor-prognosis chemo-resistant cases could potentially obscure any beneficial immune-mediated effect of allogeneic transplantation.

More direct evidence of clinically relevant graft-*versus*-malignancy activity in haematological neoplasms has come from the demonstration of tumour regression after withdrawal of immune suppression or the infusion of donor lymphocytes (DLI) following allogeneic transplantation. However, data

specifically addressing the efficacy of these approaches according to lymphoma subtype are relatively scarce (Table I).

Although the precise mechanisms behind the decrease in relapse rates remain unknown, it is this feature that fuels allogeneic transplantation programmes. The mechanisms are, however, of some relevance to the evolution of transplantation strategies. The recognition that GvT activity may be important in some haematological malignancies has resulted in the development of preparative regimens that are less myelosuppressive but more immunosuppressive, often incorporating fludarabine. The latter ensures reliable engraftment rates, whilst the former potentially reduces transplant-related mortality (TRM). This allows application to a broader patient group, including those who have previously undergone autologous transplantation. Since these approaches result in less direct anti-tumour activity, they may be less effective in the more aggressive malignancies. They have evolved within a spectrum varying in the intensity of conditioning (cytoreductive capacity) and immunosuppressive activity. Some are truly non-myeloablative, whilst others would fulfil criteria for a conventional myeloablative regimen. Most reduced intensity protocols can be assigned to one of two basic strategies. The first uses moderate conditioning with low-dose total body irradiation (TBI) or relatively modest combinations of purine analogues and alkylating agents without TCD, and the second

Table I. DLI responses.

Disease	Reference	Number	Responses	Duration	Comments
LG-unspecified	Morris <i>et al</i> (2004)	9	7 (CR or PR)	Not stated	Three treated for MRD; one 'transient'; includes CLL
FL	Mandigers <i>et al</i> (2003)	4	3 (3 CR)	43–89+ Months	
	Marks <i>et al</i> (2002)	13	8 (8 CR)	21–39+ Months	Prior anti-tumour therapy in an undisclosed number
SLL	Bernard <i>et al</i> (1999)	1	1 (CR)	24+ Months	
	Mandigers <i>et al</i> (2003)	2	2 (1 CR, 1 PR)	17–49+ Months	
CLL	Bernard <i>et al</i> (1999)	1	1 (1 PR)		Transient
	Schetelig <i>et al</i> (2003)	6	1 (CR)	26+ Months	
	Khoury <i>et al</i> (2004a)	7	6 (4 CR, 2 PR)	Not stated	5 (3 CR, 2 PR) also received rituximab
	Rondon <i>et al</i> (1996)	1	1 (CR)		
PLL	Toze <i>et al</i> (2000)	1	0		
	Ritgen <i>et al</i> (2004)*	3	2 (Molecular CR)	Not stated	Unmutated VH gene, treated for MRD
	Marks <i>et al</i> (2002)	7	1 (PR)	Not stated	
	Dreger <i>et al</i> (2003)	12	4 (3 CR, 1 PR)	Median 8 months	
	van Besien <i>et al</i> (1997)	1	0		
MCL	Peggs <i>et al</i> (2004)	1	0		B-PLL
	Marks <i>et al</i> (2002)	1	1 (CR)	23+ Months	T-PLL
DLCL	Khoury <i>et al</i> (2003)	2	1 (CR)	45+ Months	
	Morris <i>et al</i> (2004)	2	1	Not stated	
	Adkins <i>et al</i> (1998)	1	0		
	Corradini <i>et al</i> (2002)	1	0		
PTCL	Collins <i>et al</i> (1997)	6	0		Reported no significant sustained responses
	van Besien <i>et al</i> (1997)	2	0		
	Branson <i>et al</i> (2002)	3	0		Histology reported as 'high grade'
PTCL	Corradini <i>et al</i> (2004)	3	2 (1 CR, 1 PR)	Not stated	

*These cases may have also been reported in the study by Dreger *et al* (2003).

LG, low grade; FL, follicular lymphoma; SLL, small lymphocytic lymphoma; CLL, chronic lymphocytic leukaemia; PLL, pro-lymphocytic leukaemia; MCL, mantle cell lymphoma; DLCL, diffuse large cell lymphoma; PTCL, peripheral T-cell lymphoma.

combines more intensive doses of melphalan or busulphan with *in vivo* TCD [with either anti-thymocyte globulin (ATG) or alemtuzumab]. Currently, the reduced incidence of GvHD and its associated TRM achieved with the latter seems to balance the increased infective complications and relapse rates documented with TCD (Perez-Simon *et al*, 2002). Whether the judicious use of DLI can tip the balance in favour of TCD approaches remains unclear (Peggs *et al*, 2004). Current applications of DLI incur the development of GvHD, which may balance the morbidity of that associated with non-TCD approaches. The importance of a direct role of serotherapy in anti-tumour responses (e.g. alemtuzumab in the low grade CD52-expressing malignancies) also remains unclear.

Differences in outcome according to histology are likely to occur and these will probably vary between protocols relating to intensity and whether or not TCD is incorporated. Advances in our understanding of the histological subtypes of lymphoma complicate interpretation of the published literature detailing results of allogeneic stem cell transplantation for lymphoma. Based on an advancing use of molecular diagnostics we are now able to define lymphomas at an increasingly complex level according to the cell lineage and stage of cell development. This has led to an increased understanding of the response and relapse characteristics of distinct disease entities. One of the immediate effects of the evolution of lymphoma classification systems is that interpretation of historical transplant series in which lymphoma may have been categorized according to histological grade (Kiel classification) or clinical aggressiveness (International Working Formulation) becomes more challenging. In addition, the parallel refinement and development of non-transplant options provides an ever-changing standard of care by which to judge allogeneic transplantation outcomes. The aim of this review is to critically evaluate available evidence for the current position of allogeneic transplantation in the management of patients with lymphoma. In cases where series have been updated and expanded an attempt has been made only to reference the more recent data in order to prevent dual reporting of patients from the earlier cohorts. Studies that were not analysed according to histological subtype have largely been excluded.

Disease-specific outcomes

Follicular and small lymphocytic lymphomas

Whilst it is now recognized that small lymphocytic lymphoma (SLL) is biologically more akin to chronic lymphocytic leukaemia (CLL) than follicular lymphoma (FL), the majority of published transplant series have included SLL cases with the FL group, whilst larger series of CLL have been reported separately. Thus for the purpose of this review of clinical outcomes we have similarly divided the discussion of disease entities along these lines. The relatively long survival of patients with indolent low-grade lymphomas with conventional treatment, combined with the older age at diagnosis has

limited the number of allogeneic transplants performed in these conditions. Advances in non-transplant therapies, such as the development of rituximab have continued to limit their application. However, younger patients with recurrent advanced stage disease have relatively poor prognoses (median 4–5 years) and these have been the focus of allogeneic series.

Conventional allogeneic transplantation. A group of 26 patients with a median age of 42 years transplanted for low grade lymphoma [16 FL, two SLL, seven CLL, one prolymphocytic lymphoma (PLL)] between 1985 and 1998 was reported from British Columbia (Toze *et al*, 2000). Eleven had chemo-resistant disease at the time of transplantation, and 11 had previously received fludarabine. The majority ($n = 23$) underwent TBI-based conditioning. The donor source was human leucocyte antigen (HLA)-matched sibling in 19, matched unrelated in six and syngeneic in one. Actuarial TRM was 30% at 2 years. With a median follow-up of 2.4 years, the OS and event-free survival (EFS) were 58 and 54% respectively (with no significant differences between the patients with FL/SLL and those with CLL). No disease recurrences occurred after the first year. A group of 24 patients (median age 44 years) with FL undergoing T-cell replete allogeneic haematopoietic stem cell transplantation (HSCT), mainly from sibling ($n = 23$) donors, achieved an OS and progression-free survival (PFS) of 78% with a median of 2.3 years follow-up (Forrest *et al*, 2002). TRM was 21% at 2 years. The majority ($n = 22$) received busulphan-based conditioning. Only one was chemo-resistant at the time of transplantation.

Similar results were achieved with a T-cell depleted TBI-based protocol using HLA-matched sibling donors in 15 patients with poor-risk low-grade NHL (defined as relapse within 12 months after or progression during prior treatment) (Mandigers *et al*, 1998). Thirteen had FL and two had SLL. The median patient age was 47 years. At a median follow-up of 3 years, 10 patients were alive and in complete remission (CR). Two of them had relapsed after bone marrow transplantation (BMT) but re-entered CR following DLI. Five patients died from non-relapse causes.

Comparison with autologous transplantation. Twenty-eight patients undergoing TBI-based HSCT were included in a comparative single institution study (Verdonck *et al*, 1997). Eighteen underwent autologous and 10 patients allogeneic transplantation. All of the former were chemo-sensitive at the time of transplantation, whilst seven of the latter were chemo-resistant. In addition, all of the allogeneic transplant recipients had overt lymphoma infiltration of the bone marrow at the time of transplantation. All allogeneic transplant recipients achieved CR, three patients had a treatment-related death, and seven patients were alive and disease-free with a median follow-up of 41 months. In contrast, none of the autologous transplant recipients died of transplant-related complications. However, despite the fact that all autologous BMT patients had

chemo-sensitive disease only three of 18 patients remained alive and disease-free. The probability of relapse or disease-progression among allogeneic transplant patients was 0% compared with 83% for autologous transplant patients ($P = 0.002$). PFS rates at 2 years were 68% for allogeneic transplant patients and 22% for autologous transplant patients ($P = 0.049$).

A study from the International Bone Transplant Registry/Autologous Blood and Marrow Transplant Registry (IBMTR/ABMTR) compared outcomes in 176 patients with FL who had undergone HLA-identical sibling allogeneic HSCT with 728 (131 purged, 597 unpurged) who had undergone autologous HSCT (van Besien *et al*, 2003). All allograft procedures followed conditioning with conventional ablative regimens. Five-year OS rates were not significantly different between allogeneic (51%) and autologous (62% purged, 55% unpurged) cases. Although a higher TRM was documented in the allogeneic group (30% allogeneic *versus* 14% in the purged and 8% in the unpurged autologous transplants) resulting in an inferior early outcome, the reduced relapse rate in this group resulted in an apparently superior 5-year DFS (45% vs. 39% in the purged and 31% in the unpurged autologous group). Neither acute nor chronic GvHD appeared to significantly reduce the relapse risk in the allogeneic HSCT group. The lack of late recurrences in the allogeneic group (only 2% beyond 1 year) and apparent plateau on the survival curves supports the premise that allogeneic HSCT offers the potential of cure. Year of transplant was found to significantly influence OS in the allogeneic cohort. In the most recent cohort (transplanted 1997–99, $n = 52$) the 2-year OS was approximately 70%. It is important to recognize that this is a better comparator to other treatment modalities than more historical data. Age over 40 years was found to be an independent predictor of adverse outcome.

A European Bone Marrow Transplant Group (EBMT) comparative study including 231 allograft recipients with low grade histology (not further specified), matched 1–3 with autologous transplant patients, reported a similar 4-year PFS of 42.7% (Peniket *et al*, 2003). At the time of transplantation 20% of the allograft recipients had chemo-resistant disease. There was no significant difference in PFS between the allogeneic and autologous cohorts, although the relapse rate was again lower in the allogeneic group with survival curves more suggestive of a plateau than those displayed for the autologous transplant patients.

Reduced intensity transplantation. Twenty patients with either FL or SLL undergoing reduced intensity transplantation with a regimen combining fludarabine with cyclophosphamide were reported to have a 2-year actuarial DFS of 84% (Khouri *et al*, 2001). All were chemo-sensitive at the time of transplant (12 CR). Nine received rituximab in addition to the other agents. The rates of acute grade II–IV GvHD were relatively low (20%) with tacrolimus/methotrexate GvHD prophylaxis but the cumulative incidence of chronic GvHD was high (64%). The

results appear initially very promising but the limited follow-up (median 21 months), chemo-sensitive nature of this cohort, and relatively indolent nature of the disease in this selected patient group warrant that further follow-up is needed to confirm the promise of this approach.

A series including 28 patients with low-grade NHL (histology unspecified) receiving a more intensive BEAM [BCNU (carmustine), etoposide, cytarabine, melphalan]-alemtuzumab preparative regimen revealed similarly encouraging results (Faulkner *et al*, 2004). The cohort included five patients with transformed disease. Disease status at transplantation was not available specifically for this group. OS at 3 years can be estimated at 70% from the survival curves. Other survival data are only available for the entire cohort of 65 patients with lymphoproliferative disorders. The 12-month actuarial TRM was 8% in those not previously treated with an autograft. However, in keeping with the more intensive nature of the conditioning, it was 57% in those who had previously had an autograft. In addition there was a significant difference in EFS between those aged over 46 years and those under 46 (3-year EFS 38.7% vs. 77.6% respectively, $P = 0.005$). A less intensive T-cell depleted protocol incorporating fludarabine, melphalan and alemtuzumab appears to have a more acceptable toxicity profile following prior autologous transplantation (Branson *et al*, 2002). In a group of 38 patients with a variety of lymphoproliferative disorders the 2-year TRM was 20%. In an overlapping cohort of 41 patients with low-grade lymphoproliferative disorders (29 FL, nine CLL/PLL, three lymphoplasmacytoid lymphoma), 15 of whom had failed a prior autologous transplant, the 2-year TRM was 11% (Morris *et al*, 2004). Only one was chemo-resistant at the time of transplantation (11 CR). The 3-year actuarial probability of relapse was relatively high at 44%, but a number of these patients were responsive to further immune manipulation (withdrawal of immune suppression and DLI). The 3-year OS and current PFS (with DLI responsive patients included as currently non-progressive) was 73% (78% for those with sibling donors, 56% with unrelated donors) and 65% respectively.

Registry data from the EBMT on 52 patients with low grade NHL (FL and SLL) undergoing reduced intensity transplantation are also encouraging although limited by lack of follow-up (Robinson *et al*, 2002). The majority (85%) were chemo-sensitive at the time of transplantation. The median number of lines of prior therapy was 3 (range 1–5) and 29% had failed a prior autograft. TRM was 22% at 1 year. The OS and PFS were 65 and 54%, respectively, at 2 years.

Donor lymphocyte infusions. Mandigers *et al* (2003) reported seven patients with FL ($n = 5$) or SLL ($n = 2$) receiving DLI for relapsed disease following a T-deplete myeloablative allograft. Four had preceding chemotherapy, making interpretation of cause of response particularly difficult in two of the cases. Four of the remaining five responded (all CR), with apparent durability (43–89 months). A multi-institution study from the UK reported CR in eight of 13

patients with FL receiving DLI following reduced intensity transplants, although an undisclosed number received anti-tumour therapy prior to DLI (Marks *et al*, 2002). Responses were maintained at 21–39 months. It is encouraging that CR has been documented in 13 of 21 (62%) cases reported from a number of studies (Table 1).

Summary. In lymphomas where dose escalation alone fails to result in long-term DFS (FL, SLL) the minimal late recurrence rates following allogeneic transplantation are very encouraging but have not translated into improved OS. Approaches to limit TRM may make allografting the treatment of choice for such patients if HLA-identical siblings are available. The evidence available from DLI data suggests that these may be a group of disorders in which immune-mediated graft-versus-lymphoma (GvL) effects are likely to be important. Preliminary results with reduced intensity preparative regimens are very encouraging. Prospective studies comparing standard therapies (potentially autografting) with reduced intensity allogeneic transplantation earlier in the treatment pathway are warranted. In the first instance these might be limited to those with matched sibling donors. The lack of long-term follow-up in reduced intensity studies coupled with the very low late relapse rates in a number of the full intensity allograft studies warrants that younger patients (perhaps below the age of 35 or 40 years) with relatively low predicted TRM rates following more intensive preparative regimens, be seriously considered for conventional TBI-based transplants. Patients beyond second response may be considered appropriate candidates for reduced intensity approaches using sibling or unrelated donors. Current data suggest that TCD may improve results for the latter but further study is required.

Chronic lymphocytic leukaemia

The average survival for patients with advanced stage CLL is approximately 5 years and >90% of young patients will ultimately die of causes directly related to their disease. The median survival of young patients (<56 years) unresponsive to fludarabine ($n = 42$) has been reported as 48 weeks, with only 11% responding to subsequent therapies (Seymour *et al*, 1995). The median survival of patients relapsing following a fludarabine-induced remission ($n = 49$) was 87 weeks, and 83% of those who had received fludarabine as their first therapy ($n = 14$) responded to further fludarabine-containing therapies, with 60% alive at 4 years.

Conventional allogeneic transplantation. Early experience with allogeneic transplantation in patients with heavily pretreated disease demonstrated high non-relapse mortality rates but the suggestion of a plateau on survival curves. Twenty-three patients with CLL transplanted between 1988 and 1997 using stem cells from related ($n = 20$) or unrelated donors ($n = 3$) were reported from Omaha (Pavletic *et al*, 2000a). The median patient age was 46 years. At transplantation 14 patients had

chemo-refractory disease. The preparative regimen included TBI in 22 cases. GvHD prophylaxis was with cyclosporine and methotrexate. Twenty patients (87%) achieved a CR. The incidence of grade II–IV acute GvHD was 54%. Nine patients (39%) have died, including only one with progressive disease. The projected 5-year failure-free survival (FFS), OS, and relapse rates were 65, 62, and 5% respectively.

Data on a similar group of 25 patients with CLL transplanted between 1980 and 1999 have been reported from Seattle (Doney *et al*, 2002). The median patient age was 47 years. Twenty-one donors were HLA-identical siblings, one was a DR-mismatched sibling, and three were identical twins. Two patients died of recurrent CLL. Fourteen of 24 evaluable patients died of non-relapse causes. Non-relapse mortality at day 100 was 57% for the seven patients conditioned with busulphan/cyclophosphamide and 17% for the 18 patients conditioned with TBI-containing regimens. Actuarial survival at 5 years for the entire cohort was 32%. However, all patients who received busulphan/cyclophosphamide died within 3 years of transplant. OS was 48% at 5 years for the 18 patients receiving a TBI-based regimen, and was 56% for the 14 of these transplanted since 1992.

Twenty-eight patients with CLL who were either refractory to ($n = 19$) or had progressed after a prior response to fludarabine underwent allogeneic transplantation following conditioning with cyclophosphamide and TBI were reported from the MD Anderson group (Khouri *et al*, 2002). The median age was 43 years. Twenty had an HLA-identical sibling, one a single-antigen mismatched sibling, and seven a matched unrelated donor. The median follow-up for the surviving patients was 66 months. The 5-year OS and PFS was 45 and 42% respectively. The OS for the chemo-sensitive patients was 78%, compared with 31% for those with refractory disease ($P = 0.05$). PFS at 5 years was 78% for the chemo-sensitive and 26% for the chemo-refractory patients ($P = 0.03$). Eight patients died of transplant-related causes. The actuarial risk of acute grade II–IV GvHD was 49% and of chronic GvHD was 64%.

Registry data. Data on 209 patients from the EBMT undergoing allogeneic transplantation for CLL have been reported in abstract form (Michallet *et al*, 2001). A relatively high TRM of 40% impacted significantly on overall outcomes. The projected 3-year survival was 55% (compared with 79% in an autologous transplant group of 482 patients, $P < 0.01$). However, only 90 of the allograft group could be evaluated for disease response. Similar outcomes were reported from the IBMTR (Horowitz *et al*, 2000). In a group of 204 patients with a median age of 47 years the projected 3-year OS was 45%. The usual caveats apply to interpretation of registry data (selection of poor-risk patients with extensive pretreatment for allografting, improvements in supportive care, more recent reductions in GvHD incidence). Improvements in HLA-typing, GvHD prevention and supportive care allow application of unrelated donor transplants to younger

patients with CLL. Data available from 33 patients transplanted from unrelated donors reported to the National Marrow Donor Program revealed a 3-year DFS of 44% (Pavletic *et al*, 2000b).

Reduced intensity transplantation. A reduced intensity approach based on a combination of fludarabine and cyclophosphamide, with subsequent incorporation of rituximab to enhance tumour control after the initial seven patients, has been reported in 17 patients with CLL and HLA-identical sibling donors (Khouri *et al*, 2004a). The median age was 54 years. All patients were either refractory to fludarabine or had recurrence following prior fludarabine therapy (eight were chemo-sensitive at the time of transplantation). The study schema was designed to maximize the chance of GvL activity in those with persistent or progressive disease by early taper and discontinuation of tacrolimus followed by rituximab and DLI (with relatively high T-cell doses) in those patients not developing GvHD. Given this design the high incidence of GvHD (60% chronic) was not unexpected. Four patients died of chronic GvHD and a further patient died of infection and GvHD (2-year TRM 22% but still rising). The response rates following immuno-manipulation were encouraging, although the absolute contribution of the additional cytoreductive serotherapy is impossible to gauge. Similarly, the documentation of 12 cases of CR at best response also provides some evidence for optimism, although all five cases that died of GvHD-related causes were within this group. The estimated OS and PFS at 2 years were 80 and 60% respectively. However, a progressive fall in the PFS curve beyond this time point is evidenced by three deaths at later time points and there is as yet no clear evidence of a plateau. Although there was a suggestion that the group treated with the rituximab-containing conditioning regimen achieved superior results, this group had more chemo-sensitive cases (60% vs. 29%) and achieved less CRs (60% vs. 86%). A comparison with a historical group of patients with CLL treated at the same institution (median age 47 years) revealed comparable survival rates at 2 years (PFS 60% for the reduced intensity group *versus* 44%, $P =$ not significant). Further follow-up is required in order to confirm a plateau on current survival curves.

A relatively small number of CLL patients ($n = 7$) were included in the series of reduced intensity HLA-matched sibling allograft recipients reported following conditioning with low dose single-fraction TBI (McSweeney *et al*, 2001). Fludarabine was added to the conditioning protocol after a high graft failure rate in initial patients. The median age was 54 years. Of the entire cohort of CLL patients one rejected, one died of infection and one of disease progression. Four remained alive and progression-free at 319–528 d post-transplant. Two attained molecular CRs, the slow tempo of which suggested the activity of GvL mechanisms. In a group of 13 CLL and PLL patients conditioned with BEAM-alemtuzumab included in a larger series of patients with lympho-proliferative

disorders, the 2-year OS and EFS were both 69% (Faulkner *et al*, 2004).

The Cooperative German Transplant Study Group reported the outcome of 30 patients with CLL using a reduced intensity approach incorporating fludarabine, busulphan and anti-thymocyte globulin (Schetelig *et al*, 2003). Fifteen had a related and 15 an unrelated donor. At the time of transplantation 46% were chemo-refractory and the median age was 50 years. TRM was 15% at 2 years. Acute GvHD was relatively common despite the *in vivo* TCD, although this mainly reflected a high level in those with unrelated donors (grade II–IV in 27% related, and 87% unrelated donor recipients). The inclusion of ATG in this protocol appeared to have no major impact on the rate of acute GvHD in the HLA-identical sibling setting (Schetelig *et al*, 2004). Chronic GvHD occurred in 75% of cases. Despite a relatively intensive protocol and high incidence of chronic GvHD only 40% attained a CR. Six of the 12 patients who achieved a CR were refractory to fludarabine prior to transplantation. Relatively few patients were eligible for DLI because of the high GvHD rates. Only one of six (a patient with low level disease) had a durable response to DLI. The 2-year OS and PFS was 72 and 67% respectively.

To date there is relatively little data to address the issue of whether the potential GvL effect of allogeneic transplantation can overcome the prognostic influence of the newer markers of adverse biological disease characteristics [unmutated VH gene status, CD38 and zeta-chain-associated protein 70 (ZAP-70) expression, del 11q23 or del 17p13]. These remain adverse prognostic factors with dose escalation (Ritgen *et al*, 2003), although autologous transplantation may confer a relatively large absolute survival advantage in this poor-prognosis group (Dreger *et al*, 2004). Preliminary experience with reduced intensity transplantation (fludarabine and cyclophosphamide) in patients with unmutated VH gene status indicated that a minimal residual disease (MRD) negative state could be achieved in seven of nine cases (occurring from day 100 onwards subsequent to chronic GvHD or DLI) compared with only six of 26 control patients after autologous transplantation, providing optimism for the role of immunotherapy in the management of this group (Ritgen *et al*, 2004).

Seventy-seven patients with CLL treated with reduced intensity allografts between 1998 and 2001 were identified in a recent EBMT study (Dreger *et al*, 2003). The median age was 54 years. Sixty-two had an HLA-identical sibling donor. Interpretation is complicated by the multiplicity of conditioning regimens. Forty per cent had some form of TCD with either ATG or alemtuzumab. Status at transplant was CR in eight, partial remission (PR) in 42 and less than PR in 27. The TRM at 12 months was 18%, and the 2-year EFS and OS was 56 and 72% respectively. The 2-year probability of progression or relapse was 31%. Achievement of CR ($n = 53$, 69%) was significantly associated with the development of chronic GvHD, and only one patient had disease progression following development of chronic GvHD, compared with 14 of 33

without chronic GvHD ($P < 0.0001$). Further support for a GvL effect was provided by a number of responses to DLI. Responses were documented in four of 12 patients given DLI for insufficient disease control (three CR, one PR). Multivariate analyses identified disease response at transplant and the use of unrelated donors as adverse factors for relapse. TCD was not significantly associated with overall relapse risk, although it was associated with an increased relapse risk at time points beyond 1 year post-transplantation.

Donor lymphocyte infusions. Responses were documented in 15 of 37 patients with CLL (41%) treated with DLI reported in the literature (Table I). Inclusion of case reports probably results in a positive selection bias. However, complete responses were documented in 11 (30%) including molecular CR in at least four of five of those assessed, confirming the existence of a graft-versus-leukaemia activity in CLL.

Summary. Similar considerations apply to those outlined for FL/SLL. Although outcomes following allogeneic transplantation may seem worse for CLL in some series compared with those for FL/SLL, this probably reflects the inclusion of greater numbers of chemo-refractory cases (Table II). When analysis is restricted to chemo-sensitive cases the results appear comparable. Thus further exploration of reduced intensity approaches is warranted, but ablative conditioning may still have a role in younger patients.

Richter's syndrome

Transformation in CLL is associated with a grim prognosis (median survival of <8 months) (Tsimberidou *et al*, 2003). Experience with allografting is limited. Of a small series of eight patients, three remained alive and in remission at 14–67 months post-transplant (Rodriguez *et al*, 2000). At the time

of transplant, five were chemo-resistant and three chemo-sensitive or untested relapse. The preparative regimen varied. Four received an ablative chemotherapy-based regimen and four a range of less intensive regimens. Five died of transplant-related causes. The application of a reduced intensity approach incorporating alemtuzumab in three patients with Richter's transformation resulted in disappointing outcomes (Khouri *et al*, 2004b). Despite the potential for direct anti-tumour activity of the anti-CD52 monoclonal drug, one patient died of progressive disease at 6 months, and one had progressed by 4 months. The other died of infection at 3 months. Disease status at transplant (one partial response, one stable disease and one progressive) may in part explain these disappointing results. A case report of a patient transplanted for CLL, and subsequently relapsed with Richter's transformation, who responded to withdrawal of immune suppression and DLI has been reported (Espanol *et al*, 2003). Although no molecular studies were performed to confirm clonality, the tumour cells did not express Epstein-Barr virus (EBV)-encoded latent membrane protein 1, suggesting that this was not an EBV-driven lympho-proliferation.

Diffuse large cell lymphoma

Patients with diffuse large cell lymphoma (DLCL) in chemo-sensitive first relapse have a 40–50% chance of long-term DFS following autologous transplantation (Philip *et al*, 1995). This approach may also confer a survival advantage for high-risk patients in first CR (Haioun *et al*, 1997). However, patients with poorer predicted outcomes, such as those with residual disease on functional imaging prior to autografting (Spaepen *et al*, 2003) can be identified. Patients relapsing following an autograft have a particularly poor prognosis with a median survival of less than 12 months (Vose *et al*, 1992; Paltiel *et al*, 2003).

Table II. Transplant series: CLL.

	Number (n)	Age (years)	Number of refractory (%)	Sib/UD	NRM	OS	PFS
Conventional							
Pavletic <i>et al</i> (2000a)	23	46	61	20/3	17% at 100 d	65% at 5 years	62% at 5 years
Doney <i>et al</i> (2002)	25	47	64	25*/0	14/24 (time NA)	32% at 5 years	NA
Khouri <i>et al</i> (2002)	28	43	67	21/7	11% at 100 d	45% at 5 years	42% at 5 years
Michallet <i>et al</i> (2001)	209	47	44	NA	40% at 3 years	55% at 3 years	NA
Horowitz <i>et al</i> (2000)	242	47	NA	189/53†	30% at 3 years	45% at 3 years	NA
Pavletic <i>et al</i> (2000b)	40	44	50	0/40	33% at 100 d	41% at 3 years	44% at 3 years (n = 33)
Reduced intensity							
Dreger <i>et al</i> (2003)	77	54	35	62/15	18% at 1 year	72% at 2 years	56% at 2 years
Schetelig <i>et al</i> (2003)	30	50	46	15/15	15% at 2 years	72% at 2 years	67% at 2 years
Khouri <i>et al</i> (2004a)	17	54	53	17/0	6% at 1 year	80% at 2 years	60% at 2 years
Faulkner <i>et al</i> (2004)	13‡	NA	NA	NA	NA	69% at 2 years	69% at 2 years
McSweeney <i>et al</i> (2001)	7	53	57	7/0	NA	71% at 1 year	57% at 1 year

*Three syngeneic; †24 'other relative', 29 unrelated donor (UD); ‡includes PLL patient(s).
NRM, non-relapse mortality.

Conventional allogeneic transplantation. Histological identification of lymphomas as DLCL from retrospective transplantation series employing the Working Formulation is problematic. However, it can be estimated that approximately 75% of intermediate grade and 90% of high grade lymphomas (in those series excluding lymphoblastic and Burkitts subtypes) are probably DLCL. A French multi-centre study reported 5-year OS and DFS rates of 41 and 40%, respectively, in a group of 73 patients with aggressive lymphomas (including intermediate grade lymphomas, immunoblastic lymphoma and anaplastic Ki-1 positive lymphoma) (Dhedin *et al*, 1999). Thirty-nine (53%) had diffuse large cell histology (22 B-cell, eight T-cell, nine not available) and histological subtype was not a significant factor in survival analyses. The median age was relatively young (35 years). Only 10 had undergone a prior autograft. The median follow-up in surviving patients was 90 months. All but one were transplanted from HLA-identical sibling donors. Forty-six (63%) had chemo-sensitive disease (14 CR1, 11 CR2/3) and 27 (37%) bone marrow involvement at the time of transplantation. The probability of disease progression was 30% at 5 years, but only one relapse occurred beyond 15 months (a low-grade relapse in a patient transplanted for transformed disease), suggesting that the majority of the remaining patients may have been cured. The OS of the 25 patients transplanted in CR was an encouraging 76% at 5 years, and the PFS was 60% in the group of 22 patients treated in chemo-sensitive relapse. Results were relatively poor for those patients not in CR at the time of transplantation ($n = 48$). In this group, the OS was 23% at 5 years. Results for PFS, in particular for the 27 patients with chemo-refractory disease, are not available.

Comparative studies. A case-matched analysis from the EBMT including 43 patients with intermediate or high-grade lymphoma undergoing allogeneic transplantation failed to demonstrate a significant advantage in favour of allografting over autografting in terms of either PFS (43% vs. 49%) or relapse (29% vs. 35%) (Chopra *et al*, 1992). An updated analysis from the EBMT separated the intermediate ($n = 120$) and high grade ($n = 255$) patients receiving allografts and matched each with three patients receiving autografts (Peniket *et al*, 2003). At the time of transplantation 31% of the former,

and 18% of the latter were chemo-resistant. The 4-year PFS was 35 and 39%, and the TRM 42 and 33% for the intermediate and high grade lymphoma patients undergoing allogeneic transplantation respectively. PFS following autografting was not significantly different for the intermediate grade but was better for the high grade group (absolute figures not given).

Reduced intensity transplantation. There are no particularly large series exclusively reporting reduced intensity approaches in patients with DLCL (Table III). Nine patients were included in a cohort of 45 patients with a variety of haematological malignancies conditioned with thiotepa, fludarabine and cyclophosphamide (Corradini *et al*, 2002). Information on disease status at transplantation is not available. Two died prior to day 100 (one TRM, one disease progression) and a further patient had disease progression. Six remain in CR (180–850 d) with a median follow-up of approximately 20 months. Eight patients with DLCL were included in a cohort of 23 patients with lymphoma conditioned with fludarabine, busulphan and ATG (Nagler *et al*, 2000). Five had chemo-sensitive disease at the time of transplantation. Only one remains alive (at 25 months), with chronic GvHD following three DLIs for residual disease. Two of the other seven died following disease progression, and five of non-relapse mortality.

A multi-centre UK study using reduced intensity conditioning included 22 patients with DLCL (B cell immunophenotype) and 11 with transformed low-grade NHL (Morris *et al*, 2004). An additional four patients with peripheral T-cell lymphoma (PTCL) were included in the analyses of this 'aggressive NHL' group. Nineteen had failed a prior autograft. The preparative regimen consisted of fludarabine, melphalan and alemtuzumab. The 3-year actuarial OS and PFS were both 34% for the entire cohort. Actuarial PFS at 3 years for patients transplanted in CR ($n = 6$) was 50%, in chemo-sensitive PR ($n = 23$) was 37% and of those transplanted with refractory disease ($n = 8$) only one patient was progression-free at 2.5 years. Non-relapse mortality was 38% at 3 years. Relapse remained a major problem (estimated actuarial 3-year risk of 53%).

Table III. Transplant series: DLCL.

	Number (n)	Age (years)	Number of refractory (%)	NRM	OS	PFS
Conventional						
Dhedin <i>et al</i> (1999)	73 (39 DLC) – see text	35	37	44%	41% at 5 years	40% at 5 years
Reduced intensity						
Morris <i>et al</i> (2004)	22 DLC, 11 tLG, four PTCL	NA	22	38% at 2 years	34% at 3 years	34% at 3 years
Spitzer <i>et al</i> (2001)	20 DLC	38	85 (10% untested)	0% at 100 d		25% at 13–52 months
Corradini <i>et al</i> (2002)	9 DLC	NA	NA	11% at 100 d	78% at 20 months	67% at 20 months
Nagler <i>et al</i> (2000)	8 DLC	40	38	63% at 2 years	13% at 2 years	13% at 2 years

DLC, diffuse large cell; tLG, transformed low grade; PTCL, peripheral T-cell lymphoma; NRM, non-relapse mortality.

A series of 20 patients with poor prognosis diffuse large B cell lymphoma were reported in abstract form (Spitzer *et al*, 2001). Disease status at the time of transplantation was primary refractory in 7, refractory relapse in 10, untreated relapse following prior autograft in 2 and partial response in 1. Median age was 38 years. The preparative regimen consisted of cyclophosphamide, ATG or anti-CD2 antibody and thymic irradiation. Eight patients had a disease response, maintained in 5 (25%) at 13–52 months.

Donor lymphocyte infusions. Few data have been reported on the outcome of DLI in high grade lymphomas and the results have been disappointing (Table I). Whether this relates to the tempo of disease relapse or an intrinsic resistance to GvL activity remains unclear. Occasional reports of impressive and apparently durable responses to withdrawal of immune suppression have been reported (van Besien *et al*, 1997; Bierman, 2000), suggesting that there may be a potential therapeutic gain associated with immune manipulation in at least a proportion of these lymphomas.

Summary. Given the reasonable outcomes and limited toxicity of salvage high dose therapy and autologous stem cell rescue in DLBCL, allogeneic transplantation should be considered only following autograft failure unless outcome is predicted to be particularly poor. If allogeneic transplantation is considered for younger patients with high-risk features and a good performance status it should only be performed in the context of a clinical study. An alternative might be a tandem autologous-allogeneic approach (Carella *et al*, 2000). Patients with stem cell compromise because of prior therapy or bone marrow infiltration prejudicing autologous approaches may also be candidates for allogeneic approaches. Since the importance of the immune-mediated component of the transplant is less-well documented in DLBCL, but the intensity of conditioning does appear to be of importance, either a full intensity or one of the more intensive of the reduced intensity spectrum of regimens may be appropriate. Reduced intensity transplantation following a failed autograft can be considered but its use in this setting also remains investigational. The same considerations for intensity apply, although regimens such as BEAM-alemtuzumab may be too intensive in these cases (Faulkner *et al*, 2004).

Mantle cell lymphoma

This relatively uncommon disease (3–5% of NHL) is characterized by the t(11;14) cytogenetic abnormality that results in a novel fusion gene (PRAD-1/bcl-1) and overexpression of cyclin D1. The median age of presentation is 65 years. Whilst a significant proportion of cases show initial chemo-sensitivity (20–60%), early recurrence is common and average survivals of 3–4 years are reported. However, distinct differences in behaviour are reported to occur according to a number of histological features. Thus blastic histology is an unfavourable

feature (Bernard *et al*, 2001). Mantle cell lymphoma (MCL) is one of the entities that may have been classified under different categories in the Working Formulation, and historical and registry series are therefore particularly difficult to evaluate for evidence of response to allogeneic transplantation. The role of high dose therapy and autologous rescue remains unclear. Use early in the disease may improve OS but there is little evidence that the procedure is curative (Jacobsen & Freedman, 2004). The role of rituximab and of TBI-based conditioning regimens is also unclear.

Conventional allogeneic transplantation. Partly because of the advanced age of the majority of patients the numbers of allogeneic transplants performed for MCL have been very limited. An early study from the EBMT registry in heavily pretreated patients showed 2-year OS and EFS of 62% and 50%, respectively, in 22 patients undergoing allogeneic HSCT between 1983 and 1998 (Vandenberghe *et al*, 2000). Scattered reports of successful cases have appeared in the literature. Two patients remained alive and in CR at 12 months (Corradini *et al*, 1996; Adkins *et al*, 1998), another at 8 years (Kroger *et al*, 2000) and one of two at 38 months (Milpied *et al*, 1998). The 3-year OS and PFS were only 23 and 12% in 12 patients reported from Seattle (58% non-relapse mortality) (Sohn *et al*, 1998). A series of 16 patients with MCL with diffuse histology, including three with blastic features, documented a 3-year OS and EFS of 55% following allogeneic HSCT from a sibling donor (Khoury *et al*, 1999). Median patient age was 52 (range 30–60) years, and median follow-up 24 months. The estimated 3-year OS/EFS was 80% for patients with chemo-sensitive disease at the time of transplantation ($n = 10$, including five in CR1). Fourteen of the patients had been conditioned with conventional approaches (11 TBI-based), and two with a reduced intensity protocol. Of the latter, one died of progressive disease following failure of engraftment, and the other achieved CR following the onset of GvHD, suggesting the possibility of a clinically relevant GvL effect. Five died of TRM.

Reduced intensity transplantation. The largest single centre series to date reported 18 patients treated on one of two consecutive trials (Khoury *et al*, 2003). Five underwent a conditioning regimen consisting of cisplatin, fludarabine and cytarabine, and 13 a regimen consisting of fludarabine, cyclophosphamide and high-dose rituximab. Tacrolimus and methotrexate were used as GvHD prophylaxis. All had failed to achieve remission or had disease recurrence after previous therapy. Five had failed a prior autograft and 16 (89%) had chemo-sensitive disease (eight CR, eight PR; the other two had stable disease at transplantation). Thirteen had a sibling donor. There was one transplant-related death. Median follow-up was 26 months. Grade II acute GvHD occurred in 17%, grade III–IV in 0% and extensive chronic GvHD in 36%. Complete remission was maintained in the eight patients transplanted in CR, and occurred in nine of 10 of the others. Three of the latter

relapsed. Two received DLI and one was re-induced into a stable CR. Current progression-free survival (CPFS) was reported as 82% at 3 years.

Thirty-three patients with relapsed or refractory MCL who underwent reduced intensity (fludarabine/low dose single-fraction TBI) HSCT were reported in a multi-institution study (Maris *et al*, 2004). Sixteen had matched related and 17 matched unrelated donors. Thirteen (39%) had chemo-refractory disease (defined as less than PR to preceding chemotherapy). Cyclosporine and mycophenolate mofetil were used as GvHD prophylaxis. Median follow-up was 24.6 months. Non-relapse mortality was 24%, including two fatal graft rejections. Grade II acute GvHD occurred in 27%, grade III–IV in 30% and extensive chronic GvHD in 64% of evaluable patients. Disease responses were documented in 85% of those with measurable disease ($n = 20$) at transplant. Two-year OS was 64% (56% related, 74% unrelated) and PFS was 60% (56% related, 66% unrelated) at 2 years.

Some additional data on patients with MCL can also be extracted from larger series of patients with lymphoproliferative disorders undergoing reduced intensity transplantation approaches. Three-year OS and CPFS was 60 and 50%, respectively in 10 patients (nine chemosensitive, one progressive) conditioned with melphalan, fludarabine and alemtuzumab (Morris *et al*, 2004). Two of these patients received DLI for progressive disease and one responded. The more intensive T-deplete BEAM-alemtuzumab regimen resulted in a similar 3-year OS of 40% in five patients with MCL (Faulkner *et al*, 2004). Further specific details are not available on this subgroup but relapse appeared to be the major cause of treatment failure. Despite a high incidence of acute (two grade II, one grade III) and chronic (three extensive) GvHD, two of four patients with MCL from a series of patients conditioned with thiotepa, fludarabine and cyclophosphamide died of disease progression (Corradini *et al*, 2002). One of these failed to achieve a PR with DLI. The other two were documented to be in CR at 160 and 850 d post-transplant.

Data from the EBMT registry on 22 patients with MCL undergoing reduced intensity transplants is far less encouraging (Robinson *et al*, 2002). At the time of transplantation 73% had chemo-sensitive disease. PFS at 2 years was 0%. The reason for the poor outcome was a combination of high TRM (46% at 1 year) and high progression rates (48% at 1 year).

Donor lymphocyte infusions. There has been minimal experience with DLI for MCL reported in the literature. Occasional impressive responses to withdrawal of immune suppression are documented (Grigg *et al*, 1999). Two of six patients reported to receive DLI have responded (Table I).

Summary. Preliminary data in MCL indicate the ability of allogeneic transplantation to induce durable remissions. It may be a reasonable approach in those who fail to respond to initial chemotherapy or those with recurrent disease. In younger patients with relatively low predicted TRM rates a full intensity

approach remains preferable, particularly for those with blastic morphology, when it may be considered in first response. Although there is a slowly increasing body of evidence to support the potential importance of immune-mediated effects in MCL outcomes, the combined experience with reduced intensity approaches to date fails to provide convincing evidence of a plateau in survival curves. Given the lack of long-term DFS with autologous approaches the role of allogeneic transplantation in newly diagnosed patients needs to be addressed in appropriate extended phase II studies.

Peripheral T-cell non-Hodgkin lymphoma

The PTCL are a rare and heterogeneous group of disorders characterized by a relatively poor prognosis. Relapsed or refractory patients receiving salvage treatment with high dose chemotherapy and autologous transplantation have an OS and EFS/PFS of 39–48 and 32–37%, respectively, at 3–4 years (Rodriguez *et al*, 2001; Song *et al*, 2003). The results may be superior for those with anaplastic large cell histology (3-year EFS 67%, $n = 9$) (Song *et al*, 2003). No randomized studies have been performed of autologous transplantation *versus* chemotherapy specifically in this subgroup. It is uncertain what percentage of patients with relapsed PTCL can proceed to autologous HSCT, and the potential role of autologous HSCT in CR1 remains similarly unclear.

Conventional allogeneic transplantation. Very few studies have addressed the role of allogeneic HSCT in T-cell lymphomas. A retrospective series of mainly TBI-based myeloablative transplants including both T-cell ($n = 16$) and B-cell ($n = 57$) lymphomas found no significant impact of immunophenotype (T or B) on survival (Dhedin *et al*, 1999). The 5-year OS and PFS rates were 41 and 40%, respectively, for the entire cohort (76% for those in CR at the time of transplant). The analysis excluded Burkitt and lymphoblastic lymphoma. Seven of the 36 patients undergoing high dose therapy procedures for PTCL in the series reported by Rodriguez *et al* (2001) had allogeneic HSCT (mostly chemotherapy based conditioning). Four had diffuse mixed and three large cell histology (none anaplastic). Only four were chemosensitive at the time of transplant (one CR, three progressive). The 3-year OS and PFS rates were 29 and 14% in this group (compared with 39 and 32% in those undergoing autologous HSCT). Four died as a result of TRM in CR.

Reduced intensity transplantation. As in other lymphoma subtypes, reduced intensity approaches are now being explored. A series of 17 patients with relapsed or refractory PTCL received salvage chemotherapy prior to a thiotepa, cyclophosphamide and fludarabine-containing reduced intensity conditioning protocol (Corradini *et al*, 2004). Sixteen had a sibling and one an unrelated donor. Eight had failed a previous autologous HSCT. At the time of transplant

two were in CR, 12 PR, one untested relapse and two had primary chemotherapy-refractory disease. Six developed acute (four grade I–II, two grade IV) and seven chronic GvHD. Three received DLI for progressive disease. Two responded (one CR, one PR). With a median follow-up of 28 months 12 remained in CR. Estimated 3 year OS and PFS were 81 and 64%. This study provides some evidence to support the existence of a GvL effect against PTCL. Six patients with PTCL were included in the study of BEAM-alemtuzumab (Faulkner *et al*, 2004). Only limited data are available on this subgroup but the 3-year OS was 100%.

Summary. Similar considerations as those detailed for DLBCL for the role of allogeneic transplantation apply to PTCL, although the role of autologous transplantation is less clear. Studies examining the role of reduced intensity approaches earlier in the disease course for those with poor-risk features or chemo-sensitive relapse are warranted.

Burkitt and lymphoblastic lymphoma

Both Burkitt/Burkitt-like (BL) and lymphoblastic (LBL) lymphomas have leukaemic counterparts and are often treated with similarly aggressive regimens. Both are relatively common amongst paediatric lymphomas but account for <5% of NHL cases in adults. Despite high initial response rates these lymphomas have historically often recurred. Results of allogeneic transplantation in this setting have been disappointing. An encouraging series reported continuing CR in seven of nine patients with BL (transplanted in CR1) at 18–59 months post-transplant (Troussard *et al*, 1990). However, this report was from 1990 and marked improvements in outcomes following conventional chemotherapy in this group have probably negated much of the initial benefit of dose escalation achieved with earlier transplantation approaches. Ten patients with BL were included in a series of 64 patients with relapsed/refractory lymphoma from the MD Anderson Cancer Center (van Besien *et al*, 1996). Seven progressed within 2 months and there was only one long-term survivor. The same series included 25 heavily pretreated patients with LBL. The 2-year OS and DFS was 21 and 17% respectively.

Comparison with autologous transplantation. A relatively small French analysis described a trend towards a survival advantage for allogeneic ($n = 12$) over autologous ($n = 18$) transplantation for a group of high-risk patients with lymphoblastic lymphoma transplanted in first remission ($P = 0.06$). Either transplantation approach conferred a survival advantage over no further therapy following induction chemotherapy (OS 60% vs. 30%, $P = 0.005$) (Bouabdallah *et al*, 1998).

A recent EBMT study included 314 patients with lymphoblastic and 71 with Burkitt's morphology undergoing allogeneic transplantation between 1982 and 1998 (Peniket *et al*, 2003). The vast majority (almost 90%) had HLA-identical sibling

donors. Chemo-resistance at the time of transplantation was documented in 12.1 and 20% of the lymphoblastic group and the Burkitt's group respectively. The actuarial 4-year PFS was 37.7% in the lymphoblastic group and 34.9% in the Burkitt's group. Matched groups undergoing autologous transplantation (matched three autologous to one allogeneic patient) had superior OS and PFS survival rates, with late relapses uncommon in either group. Although an attempt was made to match for year of transplant it could not exclude a possible difference between the cohorts in terms of improvements in TRM and survival outcomes over time. Multiple studies have demonstrated such an effect in allogeneic transplant groups (Gahrton *et al*, 2001; van Besien *et al*, 2003) that in absolute terms will outweigh improvements in autologous cohorts.

A comparative study from the IBMTR/ABMTR included data from 76 allograft and 128 autograft recipients with lymphoblastic lymphoma (Levine *et al*, 2003). There were no differences in lymphoma-free survival rates (5-year rate was 36% in the allograft versus 39% in the autologous cohort, $P = 0.82$), even when consideration was made for confounding factors, such as disease stage, bone marrow involvement or time from diagnosis to transplantation. The pattern of treatment failure (TRM *versus* relapse) differed between the two groups.

Summary. Outcomes with conventional chemotherapy for LBL and particularly BL have improved over the past decade. The role of both autologous and allogeneic transplantation in these disorders remains unclear. There are no convincing risk models that identify clear indications for transplantation in CR1. Allogeneic transplantation should probably therefore be restricted to chemo-sensitive relapsed patients. The outcomes with salvage chemotherapy are poor, and achievement of a stable second remission remains a major problem. Early referral for consideration of allogeneic transplantation is therefore advisable. The lack of a clear contributory benefit of GvL in these disorders suggests that for patients without bone marrow involvement in whom a sibling is not available, autologous transplantation may provide a reasonable alternative to unrelated donor transplantation, particularly if the potential delay incurred by the donor search is likely to be considerable.

Conclusions

The role of allogeneic transplantation in the management of lymphomas remains uncertain. Increasing evidence has accumulated to support the concept of a therapeutically relevant GvL effect for a number of lymphoma subtypes, and a gradual improvement in TRM rates have made these approaches more attractive. The low rates of late relapses with conventional transplant approaches support the concept of attainment of cure in a proportion of patients. Reduced intensity approaches allow application to a broader patient group, but follow-up in these studies is limited. Single centre studies suggest that

acceptable TRM rates can be achieved in younger patients with conventional cyclophosphamide/TBI based regimens. This is supported by the registry analyses of more recent time periods, and may be even more pronounced with the incorporation of TCD. In 22 chemo-sensitive patients with lymphoma (three low-, nine intermediate- and 10 high-grade) with a median age of 36 years a preparative regimen including TBI and CD6⁺ T-cell depletion resulted in a TRM of only 5% (Soiffer *et al*, 1998). The 40-month EFS and OS rates were estimated at 54 and 59% respectively. Eight relapsed at a median of 6.5 months. One of the strengths of these studies is the demonstration of very few late relapses, a feature that has yet to be confirmed in the majority of reduced intensity series. As such, it currently remains unclear whether reduced intensity approaches offer a real advantage in the younger patients in whom the predicted TRM rate with more intensive approaches may be more acceptable. It is also important to recognize that whilst allogeneic transplantation has been evaluated in a number of phase I and II studies, the results are difficult to interpret because of a lack of randomized controlled studies, and the impact of eligibility criteria and patient selection on outcome. Whilst those including larger numbers of chemo-resistant cases provide encouraging data given the extremely poor predicted outcomes in these groups, other studies have been limited to chemo-sensitive patients only. In the setting of low grade disorders the latter is particularly important if follow-up is limited. Few prospective comparative studies have been performed. Randomization is problematic given the often strongly-held preferences of the physician or patient. A relatively small study comparing autologous ($n = 35$) and allogeneic ($n = 31$) transplant modalities in patients with relapsed or refractory NHL that attempted a biological randomization by sibling donor availability reported a significant reduction in disease progression in the allogeneic cohort (20% vs. 69%, $P = 0.001$), but only a non-significant improvement in PFS (47% vs. 24%, $P = 0.21$) (Ratanatharthorn *et al*, 1994). The study design was to give 'preference' to allogeneic transplantation in those with an available donor, but bias was likely to be working in both directions, with an excess of higher risk patients with bone marrow involvement in the allogeneic group, but an excess of those with less favourable age and general medical conditions in the autologous group. Interpretation is further complicated by the inclusion of all Working Formulation lymphoma subtypes.

There is still no definitive data available to answer the question of the relative importance of graft purity and GvL to outcomes. The evidence for GvL activity is often stronger in those cases where graft contamination is more likely in the autologous setting (CLL, FL) and in which one might theorise that a tumour-free graft may be more important. In DLCL, relapse often occurs at the original extra-medullary site and the importance of a tumour-free graft is probably less, but similarly the evidence for a relevant GvL effect in these tumours is less persuasive. Data from reduced intensity series inferring that a slow tempo of disease response may be seen,

and that this may mirror reductions in immune suppression, support a major role for GvL in the low grade lymphomas and perhaps MCL. Experience with DLI in the reduced intensity setting also suggests that durable responses can be attained in the low grade disorders, even when disease bulk is significant, and this supports a probable role of GvL in those cases not receiving DLL. Further follow-up of these series may help to address these issues.

Increasingly precise and reproducible lymphoma classifications have refined our knowledge of the response and relapse characteristics of distinct disease entities. These advances, coupled with identification of new prognostic indices (e.g. immunoglobulin gene rearrangements and p53 mutation/deletion status in CLL, cytogenetic abnormalities detected by fluorescent *in situ* hybridization) enable the identification of cases likely to do poorly with conventional therapies. Additional information derived from gene array analyses is further refining these response predictions. These approaches may identify natural candidates for novel treatment strategies, and we may be able to move towards an era of individualized risk-stratified therapy. Yet it remains unclear whether further treatment intensification in these cases will improve outcome. The lessons learnt from transplantation studies in acute leukaemia may be pertinent. The poorer prognostic groups may continue to do poorly with little apparent overall benefit, whilst the standard risk groups may derive the greatest absolute benefit. However, these risk-adapted approaches provide a platform from which to design appropriate prospective studies to address these issues.

For some rare aggressive lymphomas, typified by hepatosplenic T-cell lymphomas (Belhadj *et al*, 2003), outcomes are poor with conventional chemotherapy even with dose intensification, and the literature detailing allogeneic transplantation outcomes is particularly limited. Given that many of these occur in relatively young patients, allogeneic transplantation is an attractive option if the disease is chemo-sensitive and a donor can be identified within an appropriate time frame. It is important that such cases are reported to registries regardless of outcome so that the role of transplantation can be better defined.

Approaches to the integration of allogeneic transplantation in current management algorithms for lymphoma should thus be based on a number of principles. All patients should be treated on clinical trials if possible. Appropriate timing of transplantation in the treatment pathway will vary according to histological subtype. The most appropriate preparative regimen may vary according to both disease- and patient-related factors. Donor source may also influence the timing and choice of preparative regimen. The relative merits of more or less intensive preparative regimens, and of strategies incorporating TCD need to be more clearly defined by more widespread collaborative studies. Although contentious, patients with disease that is refractory to modern salvage regimens should seldom be considered candidates for allogeneic approaches. The exception may be those patients with low

grade disorders (FL, SLL, CLL) who would be considered appropriate candidates for more intensive preparative regimens, in whom a significant minority may achieve long term DFS. Whether reduced intensity protocols confer a similar benefit in this group remains unclear.

References

- Adkins, D., Brown, R., Goodnough, L.T., Khoury, H., Popovic, W. & DiPersio, J. (1998) Treatment of resistant mantle cell lymphoma with allogeneic bone marrow transplantation. *Bone Marrow Transplantation*, **21**, 97–99.
- Belhadj, K., Reyes, F., Farcet, J.P., Tilly, H., Bastard, C., Angonin, R., Deconinck, E., Charlotte, F., Leblond, V., Labouyrie, E., Lederlin, P., Emile, J.F., Delmas-Marsalet, B., Arnulf, B., Zafrani, E.S. & Gaulard, P. (2003) Hepatosplenic gammadelta T-cell lymphoma is a rare clinicopathologic entity with poor outcome: report on a series of 21 patients. *Blood*, **102**, 4261–4269.
- Bernard, M., Dauriac, C., Drenou, B., Leberre, C., Branger, B., Fauchet, R., Le Prise, P.Y. & Lamy, T. (1999) Long-term follow-up of allogeneic bone marrow transplantation in patients with poor prognosis non-Hodgkin's lymphoma. *Bone Marrow Transplantation*, **23**, 329–333.
- Bernard, M., Gressin, R., Lefrere, F., Drenou, B., Branger, B., Caulet-Maugendre, S., Tass, P., Brousse, N., Valensi, F., Milpied, N., Voilat, L., Sadoun, A., Ghandour, C., Hunault, M., Leloup, R., Mannone, L., Hermine, O. & Lamy, T. (2001) Blastic variant of mantle cell lymphoma: a rare but highly aggressive subtype. *Leukemia*, **15**, 1785–1791.
- van Besien, K.W., Mehra, R.C., Giral, S.A., Kantarjian, H.M., Pugh, W.C., Khouri, I.F., Moon, Y., Williams, P., Andersson, B.S., Przepiora, D., McCarthy, P.L., Gajewski, J.L., Deisseroth, A.B., Cabanillas, F.F. & Champlin, R. (1996) Allogeneic bone marrow transplantation for poor-prognosis lymphoma: response, toxicity and survival depend on disease histology. *American Journal of Medicine*, **100**, 299–307.
- van Besien, K.W., de Lima, M., Giral, S.A., Moore, D.F. Jr, Khouri, I.F., Rondon, G., Mehra, R., Andersson, B.S., Dyer, C., Cleary, K., Przepiora, D., Gajewski, J.L. & Champlin, R.E. (1997) Management of lymphoma recurrence after allogeneic transplantation: the relevance of graft-versus-lymphoma effect. *Bone Marrow Transplantation*, **19**, 977–982.
- van Besien, K., Loberiza, F.R. Jr, Bajorunaite, R., Armitage, J.O., Bashey, A., Burns, L.J., Freytes, C.O., Gibson, J., Horowitz, M.M., Inwards, D.J., Marks, D.I., Martino, R., Maziars, R.T., Molina, A., Pavlovsky, S., Pecora, A.L., Schouten, H.C., Shea, T.C., Lazarus, H.M., Rizzo, J.D. & Vose, J.M. (2003) Comparison of autologous and allogeneic hematopoietic stem cell transplantation for follicular lymphoma. *Blood*, **102**, 3521–3529.
- Bierman, P.J. (2000) Allogeneic bone marrow transplantation for lymphoma. *Blood Reviews*, **14**, 1–13.
- Bierman, P.J., Sweetenham, J.W., Loberiza, F.R. Jr, Taghipour, G., Lazarus, H.M., Rizzo, J.D., Schmitz, N., van Besien, K., Vose, J.M., Horowitz, M. & Goldstone, A. (2003) Syngeneic hematopoietic stem-cell transplantation for non-Hodgkin's lymphoma: a comparison with allogeneic and autologous transplantation—The Lymphoma Working Committee of the International Bone Marrow Transplant Registry and the European Group for Blood and Marrow Transplantation. *Journal of Clinical Oncology*, **21**, 3744–3753.
- Bouabdallah, R., Xerri, L., Bardou, V.J., Stoppa, A.M., Blaise, D., Sainty, D., Maraninchi, D. & Gastaut, J.A. (1998) Role of induction chemotherapy and bone marrow transplantation in adult lymphoblastic lymphoma: a report on 62 patients from a single center. *Annals of Oncology*, **9**, 619–625.
- Branson, K., Chopra, R., Kottaridis, P.D., McQuaker, G., Parker, A., Schey, S., Chakraverty, R.K., Craddock, C., Milligan, D.W., Pettengell, R., Marsh, J.C., Linch, D.C., Goldstone, A.H., Williams, C.D. & Mackinnon, S. (2002) Role of nonmyeloablative allogeneic stem-cell transplantation after failure of autologous transplantation in patients with lymphoproliferative malignancies. *Journal of Clinical Oncology*, **20**, 4022–4031.
- Carella, A.M., Cavaliere, M., Lerma, E., Ferrara, R., Tedeschi, L., Romanelli, A., Vinci, M., Pinotti, G., Lambelet, P., Loni, C., Verdiani, S., De Stefano, F., Valbonesi, M. & Corsetti, M.T. (2000) Autografting followed by nonmyeloablative immunosuppressive chemotherapy and allogeneic peripheral-blood hematopoietic stem-cell transplantation as treatment of resistant Hodgkin's disease and non-Hodgkin's lymphoma. *Journal of Clinical Oncology*, **18**, 3918–3924.
- Chopra, R., Goldstone, A.H., Pearce, R., Philip, T., Petersen, F., Appelbaum, F., De Vol, E. & Ernst, P. (1992) Autologous versus allogeneic bone marrow transplantation for non-Hodgkin's lymphoma: a case-controlled analysis of the European Bone Marrow Transplant Group Registry data. *Journal of Clinical Oncology*, **10**, 1690–1695.
- Collins, R.H., Jr, Shpilberg, O., Drobyski, W.R., Porter, D.L., Giral, S., Champlin, R., Goodman, S.A., Wolff, S.N., Hu, W., Verfaillie, C., List, A., Dalton, W., Ognoskie, N., Chetrit, A., Antin, J.H. & Nemunaitis, J. (1997) Donor leukocyte infusions in 140 patients with relapsed malignancy after allogeneic bone marrow transplantation. *Journal of Clinical Oncology*, **15**, 433–444.
- Corradini, P., Ladetto, M., Astolfi, M., Voena, C., Tarella, C., Bacigalupo, A. & Pileri, A. (1996) Clinical and molecular remission after allogeneic blood cell transplantation in a patient with mantle-cell lymphoma. *British Journal of Haematology*, **94**, 376–378.
- Corradini, P., Tarella, C., Olivieri, A., Gianni, A.M., Voena, C., Zallio, F., Ladetto, M., Falda, M., Lucese, M., Doderio, A., Cicero, F., Benedetti, F., Rambaldi, A., Sajevo, M.R., Tresoldi, M., Pileri, A., Bordignon, C. & Bregni, M. (2002) Reduced-intensity conditioning followed by allografting of hematopoietic cells can produce clinical and molecular remissions in patients with poor-risk hematologic malignancies. *Blood*, **99**, 75–82.
- Corradini, P., Doderio, A., Zallio, F., Caracciolo, D., Casini, M., Bregni, M., Narni, F., Patriarca, F., Boccadoro, M., Benedetti, F., Rambaldi, A., Gianni, A.M. & Tarella, C. (2004) Graft-versus-lymphoma effect in relapsed peripheral T-cell non-Hodgkin's lymphomas after reduced-intensity conditioning followed by allogeneic transplantation of hematopoietic cells. *Journal of Clinical Oncology*, **22**, 2172–2176.
- Dhedine, N., Giraudier, S., Gaulard, P., Esperou, H., Ifrah, N., Michallet, M., Milpied, N., Rio, B., Cahn, J.Y., Molina, L., Laporte, J.L., Guilhot, F. & Kuentz, M. (1999) Allogeneic bone marrow transplantation in aggressive non-Hodgkin's lymphoma (excluding Burkitt and lymphoblastic lymphoma): a series of 73 patients from the SFGM database. Societ Francaise de Greffe de Moelle. *British Journal of Haematology*, **107**, 154–161.
- Doney, K.C., Chauncey, T. & Appelbaum, F.R. (2002) Allogeneic related donor hematopoietic stem cell transplantation for treatment of chronic lymphocytic leukemia. *Bone Marrow Transplantation*, **29**, 817–823.

- Dreger, P., Brand, R., Hansz, J., Milligan, D., Corradini, P., Finke, J., Deliliers, G.L., Martino, R., Russell, N., Van Biezen, A., Michallet, M. & Niederwieser, D. (2003) Treatment-related mortality and graft-versus-leukemia activity after allogeneic stem cell transplantation for chronic lymphocytic leukemia using intensity-reduced conditioning. *Leukemia*, **17**, 841–848.
- Dreger, P., Stilgenbauer, S., Benner, A., Ritgen, M., Krober, A., Kneba, M., Schmitz, N. & Dohner, H. (2004) The prognostic impact of autologous stem cell transplantation in patients with chronic lymphocytic leukemia: a risk-matched analysis based on the VH gene mutational status. *Blood*, **103**, 2850–2858.
- Espanol, I., Buchler, T., Ferrà, C., Gallardo, D., Reyes, P., Sarra, J., Domingo, A., Romagosa, V. & Granena, A. (2003) Richter's syndrome after allogeneic stem cell transplantation for chronic lymphocytic leukaemia successfully treated by withdrawal of immunosuppression, and donor lymphocyte infusion. *Bone Marrow Transplantation*, **31**, 215–218.
- Faulkner, R.D., Craddock, C., Byrne, J.L., Mahendra, P., Haynes, A.P., Prentice, H.G., Potter, M., Pagliuca, A., Ho, A., Devereux, S., McQuaker, G., Mufti, G., Yin, J.L. & Russell, N.H. (2004) BEAM-alemtuzumab reduced-intensity allogeneic stem cell transplantation for lymphoproliferative diseases: GVHD, toxicity, and survival in 65 patients. *Blood*, **103**, 428–434.
- Forrest, D.L., Thompson, K., Nevill, T.J., Couban, S. & Fernandez, L.A. (2002) Allogeneic hematopoietic stem cell transplantation for progressive follicular lymphoma. *Bone Marrow Transplantation*, **29**, 973–978.
- Freedman, A.S., Neuberger, D., Mauch, P., Soiffer, R.J., Anderson, K.C., Fisher, D.C., Schlossman, R., Alyea, E.P., Takvorian, T., Jallow, H., Kuhlman, C., Ritz, J., Nadler, L.M. & Gribben, J.G. (1999) Long-term follow-up of autologous bone marrow transplantation in patients with relapsed follicular lymphoma. *Blood*, **94**, 3325–3333.
- Gahrton, G., Svensson, H., Cavo, M., Apperly, J., Bacigalupo, A., Björkstrand, B., Blade, J., Cornelissen, J., de Laurenti, A., Facon, T., Ljungman, P., Michallet, M., Niederwieser, D., Powles, R., Reiffers, J., Russell, N.H., Samson, D., Schaefer, U.W., Schattenberg, A., Tura, S., Verdonck, L.F., Vernant, J.P., Willemze, R. & Volin, L. (2001) Progress in allogeneic bone marrow and peripheral blood stem cell transplantation for multiple myeloma: a comparison between transplants performed 1983–93 and 1994–8 at European Group for Blood and Marrow Transplantation centres. *British Journal of Haematology*, **113**, 209–216.
- Grigg, A., Bardy, P., Byron, K., Seymour, J.F. & Szer, J. (1999) Fludarabine-based non-myeloablative chemotherapy followed by infusion of HLA-identical stem cells for relapsed leukaemia and lymphoma. *Bone Marrow Transplantation*, **23**, 107–110.
- Haioun, C., Lepage, E., Gisselbrecht, C., Bastion, Y., Coiffier, B., Brice, P., Bosly, A., Dupriez, B., Nouvel, C., Tilly, H., Lederlin, P., Biron, P., Briere, J., Gaulard, P. & Reyes, F. (1997) Benefit of autologous bone marrow transplantation over sequential chemotherapy in poor-risk aggressive non-Hodgkin's lymphoma: updated results of the prospective study LNH87–2. Groupe d'Etude des Lymphomes de l'Adulte. *Journal of Clinical Oncology*, **15**, 1131–1137.
- Horowitz, M.M., Montserrat, E., Sobocinski, K., Giral, S., Khouri, I.F., Schmitz, N. (2000) Hematopoietic stem cell transplantation (SCT) for chronic lymphocytic leukemia (CLL). *Blood*, **96**, 522a.
- Jacobsen, E. & Freedman, A. (2004) An update on the role of high-dose therapy with autologous or allogeneic stem cell transplantation in mantle cell lymphoma. *Current Opinion in Oncology*, **16**, 106–113.
- Jones, R.J., Ambinder, R.F., Piantadosi, S. & Santos, G.W. (1991) Evidence of a graft-versus-lymphoma effect associated with allogeneic bone marrow transplantation. *Blood*, **77**, 649–653.
- Khouri, I.F., Lee, M.S., Romaguera, J., Mirza, N., Kantarjian, H., Korbling, M., Albitar, M., Giral, S., Samuels, B., Anderlini, P., Rodriguez, J., von Wolff, B., Gajewski, J., Cabanillas, F. & Champlin, R. (1999) Allogeneic hematopoietic transplantation for mantle-cell lymphoma: molecular remissions and evidence of graft-versus-malignancy. *Annals of Oncology*, **10**, 1293–1299.
- Khouri, I.F., Saliba, R.M., Giral, S.A., Lee, M.S., Okoroji, G.J., Hagemeister, F.B., Korbling, M., Younes, A., Ippoliti, C., Gajewski, J.L., McLaughlin, P., Anderlini, P., Donato, M.L., Cabanillas, F.F. & Champlin, R.E. (2001) Nonablative allogeneic hematopoietic transplantation as adoptive immunotherapy for indolent lymphoma: low incidence of toxicity, acute graft-versus-host disease, and treatment-related mortality. *Blood*, **98**, 3595–3599.
- Khouri, I.F., Keating, M.J., Saliba, R.M. & Champlin, R.E. (2002) Long-term follow-up of patients with CLL treated with allogeneic hematopoietic transplantation. *Cytotherapy*, **4**, 217–221.
- Khouri, I.F., Lee, M.S., Saliba, R.M., Jun, G., Fayad, L., Younes, A., Pro, B., Acholonu, S., McLaughlin, P., Katz, R.L. & Champlin, R.E. (2003) Nonablative allogeneic stem-cell transplantation for advanced/recurrent mantle-cell lymphoma. *Journal of Clinical Oncology*, **21**, 4407–4412.
- Khouri, I.F., Lee, M.S., Saliba, R.M., Andersson, B., Anderlini, P., Couriel, D., Hosing, C., Giral, S., Korbling, M., McMannis, J., Keating, M.J. & Champlin, R.E. (2004a) Nonablative allogeneic stem cell transplantation for chronic lymphocytic leukemia: impact of rituximab on immunomodulation and survival. *Experimental Hematology*, **32**, 28–35.
- Khouri, I.F., Albitar, M., Saliba, R.M., Ippoliti, C., Ma, Y.C., Keating, M.J. & Champlin, R.E. (2004b) Low-dose alemtuzumab (Campath) in myeloablative allogeneic stem cell transplantation for CD52-positive malignancies: decreased incidence of acute graft-versus-host-disease with unique pharmacokinetics. *Bone Marrow Transplantation*, **33**, 833–837.
- Kroger, N., Hoffknecht, M., Kruger, W., Zeller, W., Renges, H., Stute, N., Zschaber, R. & Zander, A.R. (2000) Allogeneic bone marrow transplantation for refractory mantle cell lymphoma. *Annals of Hematology*, **79**, 578–580.
- Levine, J.E., Harris, R.E., Loberiza, F.R. Jr, Armitage, J.O., Vose, J.M., van Besien, K., Lazarus, H.M., Horowitz, M.M., Bashey, A., Bolwell, B.J., Burns, L.J., Cairo, M.S., Champlin, R.E., Freytes, C.O., Gibson, J., Goldstein, S.C., Laughlin, M.J., Lister, J., Marks, D.I., Maziarz, R.T., Miller, A.M., Milone, G.A., Pavlovsky, S., Pecora, A.L., Rizzo, J.D., Schiller, G., Schouten, H.C. & Zhang, M.J. (2003) A comparison of allogeneic and autologous bone marrow transplantation for lymphoblastic lymphoma. *Blood*, **101**, 2476–2482.
- Mandigers, C.M., Raemaekers, J.M., Schattenberg, A.V., Roovers, E.A., Bogman, M.J., van der Maazen, R.W., De Pauw, B.E. & De Witte, T. (1998) Allogeneic bone marrow transplantation with T-cell-depleted marrow grafts for patients with poor-risk relapsed low-grade non-Hodgkin's lymphoma. *British Journal of Haematology*, **100**, 198–206.
- Mandigers, C.M., Verdonck, L.F., Meijerink, J.P., Dekker, A.W., Schattenberg, A.V. & Raemaekers, J.M. (2003) Graft-versus-lymphoma effect of donor lymphocyte infusion in indolent lymphomas relapsed after allogeneic stem cell transplantation. *Bone Marrow Transplantation*, **32**, 1159–1163.

- Maris, M.B., Sandmaier, B.M., Storer, B.E., Chauncey, T., Stuart, M.J., Maziarz, R.T., Agura, E., Langston, A.A., Pulsipher, M., Storb, R. & Maloney, D.G. (2004) Allogeneic Hematopoietic Cell Transplantation after Fludarabine and 2 Gy Total Body Irradiation for Relapsed and Refractory Mantle Cell Lymphoma. *Blood*, **104**, in press.
- Marks, D.I., Lush, R., Cavenagh, J., Milligan, D.W., Schey, S., Parker, A., Clark, F.J., Hunt, L., Yin, J., Fuller, S., Vandenberghe, E., Marsh, J., Littlewood, T., Smith, G.M., Culligan, D., Hunter, A., Chopra, R., Davies, A., Towilson, K. & Williams, C.D. (2002) The toxicity and efficacy of donor lymphocyte infusions given after reduced-intensity conditioning allogeneic stem cell transplantation. *Blood*, **100**, 3108–3114.
- McSweeney, P.A., Niederwieser, D., Shizuru, J.A., Sandmaier, B.M., Molina, A.J., Maloney, D.G., Chauncey, T.R., Gooley, T.A., Hegentbart, U., Nash, R.A., Radich, J., Wagner, J.L., Minor, S., Appelbaum, F.R., Bensinger, W.I., Bryant, E., Flowers, M.E., Georges, G.E., Grumet, F.C., Kiem, H.P., Torok-Storb, B., Yu, C., Blume, K.G. & Storb, R.F. (2001) Hematopoietic cell transplantation in older patients with hematologic malignancies: replacing high-dose cytotoxic therapy with graft-versus-tumor effects. *Blood*, **97**, 3390–3400.
- Michallet, M., Brand, R., Dreger, P., Millighan, D., Esteve, J., Kimby, E., Nicolini, F., Apperley, J., van Biezen, A., Niederwieser, D. (2001) Analysis of prognostic factors on the outcome of autologous and allogeneic stem cell transplantations (SCT) for chronic lymphocytic leukemia (CLL). *Blood*, **98**, 895a.
- Milpied, N., Gaillard, F., Moreau, P., Mahe, B., Souchet, J., Rapp, M.J., Bulabois, C.E., Morineau, N. & Harousseau, J.L. (1998) High-dose therapy with stem cell transplantation for mantle cell lymphoma: results and prognostic factors, a single center experience. *Bone Marrow Transplantation*, **22**, 645–650.
- Morris, E., Thomson, K., Craddock, C., Mahendra, P., Milligan, D., Cook, G., Smith, G.M., Parker, A., Schey, S., Chopra, R., Hatton, C., Tighe, J., Hunter, A., Peggs, K., Linch, D., Goldstone, A. & Mackinnon, S. (2004) Outcome Following Alemtuzumab (CAMPATH-1H) -Containing Reduced Intensity Allogeneic Transplant Regimen for Relapsed and Refractory Non-Hodgkin's Lymphoma (NHL). *Blood* (in press).
- Nagler, A., Slavin, S., Varadi, G., Naparstek, E., Samuel, S. & Or, R. (2000) Allogeneic peripheral blood stem cell transplantation using a fludarabine-based low intensity conditioning regimen for malignant lymphoma. *Bone Marrow Transplantation*, **25**, 1021–1028.
- Paltiel, O., Rubinstein, C., Or, R., Nagler, A., Gordon, L., Deutsch, L., Polliack, A. & Naparstek, E. (2003) Factors associated with survival in patients with progressive disease following autologous transplant for lymphoma. *Bone Marrow Transplantation*, **31**, 565–569.
- Pavletic, Z.S., Arrowsmith, E.R., Bierman, P.J., Goodman, S.A., Vose, J.M., Tarantolo, S.R., Stein, R.S., Bociek, G., Greer, J.P., Wu, C.D., Kollath, J.P., Weisenburger, D.D., Kessinger, A., Wolff, S.N., Armitage, J.O. & Bishop, M.R. (2000a) Outcome of allogeneic stem cell transplantation for B cell chronic lymphocytic leukemia. *Bone Marrow Transplantation*, **25**, 717–722.
- Pavletic, S., Khouri, I., King, R., Bierman, P., Bishop, M., Carsten, M., Giralt, S., Molina, A., Montserrat, E., Anasetti, C. (2000b) HLA-matched unrelated donor (MUD) bone marrow transplantation for B-cell chronic lymphocytic leukemia (Results from the CLL Working Group, National Marrow Donor Program). *Proceedings of the American Society of Oncology*, **19**, 4a.
- Peggs, K.S., Thomson, K., Hart, D.P., Geary, J., Morris, E.C., Yong, K., Goldstone, A.H., Linch, D.C. & Mackinnon, S. (2004) Dose-escalated donor lymphocyte infusions following reduced intensity transplantation: toxicity, chimerism, and disease responses. *Blood*, **103**, 1548–1556.
- Peniket, A.J., Ruiz de Elvira, M.C., Taghipour, G., Cordonnier, C., Gluckman, E., De Witte, T., Santini, G., Blaise, D., Greinix, H., Ferrant, A., Cornelissen, J., Schmitz, N. & Goldstone, A.H. (2003) An EBMT registry matched study of allogeneic stem cell transplants for lymphoma: allogeneic transplantation is associated with a lower relapse rate but a higher procedure-related mortality rate than autologous transplantation. *Bone Marrow Transplantation*, **31**, 667–678.
- Perez-Simon, J.A., Kottaridis, P.D., Martino, R., Craddock, C., Caballero, D., Chopra, R., Garcia-Conde, J., Milligan, D.W., Schey, S., Urbano-Ispizua, A., Parker, A., Leon, A., Yong, K., Sureda, A., Hunter, A., Sierra, J., Goldstone, A.H., Linch, D.C., San Miguel, J.F. & Mackinnon, S. (2002) Nonmyeloablative transplantation with or without alemtuzumab: comparison between 2 prospective studies in patients with lymphoproliferative disorders. *Blood*, **100**, 3121–3127.
- Philip, T., Guglielmi, C., Hagenbeek, A., Somers, R., Vander, L.H., Bron, D., Sonneveld, P., Gisselbrecht, C., Cahn, J.Y. & Harousseau, J.L. (1995) Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. *New England Journal of Medicine*, **333**, 1540–1545.
- Ratanatharathorn, V., Uberti, J., Karanes, C., Abella, E., Lum, L.G., Momin, F., Cummings, G. & Sensenbrenner, L.L. (1994) Prospective comparative trial of autologous versus allogeneic bone marrow transplantation in patients with non-Hodgkin's lymphoma. *Blood*, **84**, 1050–1055.
- Ritgen, M., Lange, A., Stilgenbauer, S., Dohner, H., Bertscher, C., Bosse, H., Stuhr, A., Kneba, M. & Dreger, P. (2003) Unmutated immunoglobulin variable heavy-chain gene status remains an adverse prognostic factor after autologous stem cell transplantation for chronic lymphocytic leukemia. *Blood*, **101**, 2049–2053.
- Ritgen, M., Stilgenbauer, S., Von Neuhoff, N., Humpe, A., Bruggemann, M., Pott, C., Raff, T., Krober, A., Bunjes, D., Schlenk, R., Schmitz, N., Dohner, H., Kneba, M. & Dreger, P. (2004) Graft-versus-leukemia activity may overcome therapeutic resistance of chronic lymphocytic leukemia with unmutated immunoglobulin variable heavy chain gene status: implications of minimal residual disease measurement with quantitative PCR. *Blood*, **104**, 2600–2602.
- Robinson, S.P., Goldstone, A.H., Mackinnon, S., Carella, A., Russell, N., de Elvira, C.R., Taghipour, G. & Schmitz, N. (2002) Chemoresistant or aggressive lymphoma predicts for a poor outcome following reduced-intensity allogeneic progenitor cell transplantation: an analysis from the Lymphoma Working Party of the European Group for Blood and Bone Marrow Transplantation. *Blood*, **100**, 4310–4316.
- Rodriguez, J., Keating, M.J., O'Brien, S., Champlin, R.E. & Khouri, I.F. (2000) Allogeneic haematopoietic transplantation for Richter's syndrome. *British Journal of Haematology*, **110**, 897–899.
- Rodriguez, J., Munsell, M., Yazji, S., Hagemester, F.B., Younes, A., Andersson, B., Giralt, S., Gajewski, J., de Lima, M., Couriel, D., Romaguera, J., Cabanillas, F.F., Champlin, R.E. & Khouri, I.F. (2001) Impact of high-dose chemotherapy on peripheral T-cell lymphomas. *Journal of Clinical Oncology*, **19**, 3766–3770.
- Rondon, G., Giralt, S., Huh, Y., Khouri, I., Andersson, B., Andreeff, M. & Champlin, R. (1996) Graft-versus-leukemia effect after allogeneic bone marrow transplantation for chronic lymphocytic leukemia. *Bone Marrow Transplantation*, **18**, 669–672.

- Schetelig, J., Thiede, C., Bornhauser, M., Schwerdtfeger, R., Kiehl, M., Beyer, J., Sayer, H.G., Kroger, N., Hensel, M., Scheffold, C., Held, T.K., Hoffken, K., Ho, A.D., Kienast, J., Neubauer, A., Zander, A.R., Fauser, A.A., Ehninger, G. & Siegert, W. (2003) Evidence of a graft-versus-leukemia effect in chronic lymphocytic leukemia after reduced-intensity conditioning and allogeneic stem-cell transplantation: the Cooperative German Transplant Study Group. *Journal of Clinical Oncology*, **21**, 2747–2753.
- Schetelig, J., Bornhauser, M., Kiehl, M., Schwerdtfeger, R., Kroger, N., Runde, V., Zabelina, T., Held, T.K., Thiede, C., Fauser, A.A., Beelen, D., Zander, A., Ehninger, G. & Siegert, W. (2004) Reduced-intensity conditioning with busulfan and fludarabine with or without antithymocyte globulin in HLA-identical sibling transplantation—a retrospective analysis. *Bone Marrow Transplantation*, **33**, 483–490.
- Schimmer, A.D., Jamal, S., Messner, H., Keating, A., Meharchand, J., Huebsch, L., Walker, I., Bengler, A., Gluck, S. & Smith, A. (2000) Allogeneic or autologous bone marrow transplantation (BMT) for non-Hodgkin's lymphoma (NHL): results of a provincial strategy. Ontario BMT Network, Canada. *Bone Marrow Transplantation*, **26**, 859–864.
- Schouten, H.C., Qian, W., Kvaloy, S., Porcellini, A., Hagberg, H., Johnson, H.E., Doorduyn, J.K., Sydes, M.R. & Kvalheim, G. (2003) High-dose therapy improves progression-free survival and survival in relapsed follicular non-Hodgkin's lymphoma: results from the randomized European CUP trial. *Journal of Clinical Oncology*, **21**, 3918–3927.
- Seymour, J.F., Robertson, L.E., O'Brien, S., Lerner, S. & Keating, M.J. (1995) Survival of young patients with chronic lymphocytic leukemia failing fludarabine therapy: a basis for the use of myeloablative therapies. *Leukemia and Lymphoma*, **18**, 493–496.
- Sohn, S.K., Bensinger, W., Holmberg, L., Press, O., Storb, R., Buckner, C.D., Appelbaum, F.R., Maloney, D.G. (1998) High dose therapy with allogeneic or autologous stem cell transplantation for relapsed mantle cell lymphoma: the Seattle experience. *Proceedings of the American Society of Oncology*, **17**, 17a.
- Soiffer, R.J., Freedman, A.S., Neuberg, D., Fisher, D.C., Alyea, E.P., Gribben, J., Schlossman, R.L., Bartlett-Pandite, L., Kuhlman, C., Murray, C., Freeman, A., Mauch, P., Anderson, K.C., Nadler, L.M. & Ritz, J. (1998) CD6⁺ T cell-depleted allogeneic bone marrow transplantation for non-Hodgkin's lymphoma. *Bone Marrow Transplantation*, **21**, 1177–1181.
- Song, K.W., Mollee, P., Keating, A. & Crump, M. (2003) Autologous stem cell transplant for relapsed and refractory peripheral T-cell lymphoma: variable outcome according to pathological subtype. *British Journal of Haematology*, **120**, 978–985.
- Spaepen, K., Stroobants, S., Dupont, P., Vandenberghe, P., Maertens, J., Bormans, G., Thomas, J., Balzarini, J., Wolf-Peeters, C., Mortelmans, L. & Verhoef, G. (2003) Prognostic value of pretransplantation positron emission tomography using fluorine 18-fluorodeoxyglucose in patients with aggressive lymphoma treated with high-dose chemotherapy and stem cell transplantation. *Blood*, **102**, 53–59.
- Spitzer, T.R., McAfee, S.L., Dey, B.R., Sackstein, R., Colby, C., Sachs, D.H., Sykes, M. (2001) Durable progression free survival (PFS) following non-myeloablative bone marrow transplantation (BMT) for chemorefractory diffuse large B cell lymphoma (B-LCL). *Blood*, **98** (suppl 1), 672a.
- Toze, C.L., Shepherd, J.D., Connors, J.M., Voss, N.J., Gascoyne, R.D., Hogge, D.E., Klingemann, H.G., Nantel, S.H., Nevill, T.J., Phillips, G.L., Reece, D.E., Sutherland, H.J. & Barnett, M.J. (2000) Allogeneic bone marrow transplantation for low-grade lymphoma and chronic lymphocytic leukemia. *Bone Marrow Transplantation*, **25**, 605–612.
- Troussard, X., Leblond, V., Kuentz, M., Milpied, N., Jouet, J.P., Cordonnier, C., Leporrier, M. & Vernant, J.P. (1990) Allogeneic bone marrow transplantation in adults with Burkitt's lymphoma or acute lymphoblastic leukemia in first complete remission. *Journal of Clinical Oncology*, **8**, 809–812.
- Tsimberidou, A.M., Kantarjian, H.M., Cortes, J., Thomas, D.A., Faderl, S., Garcia-Manero, G., Verstovsek, S., Ferrajoli, A., Wierda, W., Alvarado, Y., O'Brien, S.M., Albitar, M., Keating, M.J. & Giles, F.J. (2003) Fractionated cyclophosphamide, vincristine, liposomal daunorubicin, and dexamethasone plus rituximab and granulocyte-macrophage-colony stimulating factor (GM-CSF) alternating with methotrexate and cytarabine plus rituximab and GM-CSF in patients with Richter syndrome or fludarabine-refractory chronic lymphocytic leukemia. *Cancer*, **97**, 1711–1720.
- Vandenberghe, E., Ruiz de Elvira, C., Isaacson, P., Lopez-Guillermo, A., Conde, E., Gisselbrecht, C., Guihot, F., Schmitz, N., Goldstone, A. (2000) Does transplantation improve outcome in mantle cell lymphoma (MCL)? a study from the EBMT. *Blood*, **96**, 482a.
- Verdonck, L.F., Dekker, A.W., Lokhorst, H.M., Petersen, E.J. & Nieuwenhuis, H.K. (1997) Allogeneic versus autologous bone marrow transplantation for refractory and recurrent low-grade non-Hodgkin's lymphoma. *Blood*, **90**, 4201–4205.
- Vose, J.M., Bierman, P.J., Anderson, J.R., Kessinger, A., Pierson, J., Nelson, J., Frappier, B., Schmit-Pokorny, K., Weisenburger, D.D. & Armitage, J.O. (1992) Progressive disease after high-dose therapy and autologous transplantation for lymphoid malignancy: clinical course and patient follow-up. *Blood*, **80**, 2142–2148.
- Williams, C.D., Goldstone, A.H., Pearce, R.M., Philip, T., Hartmann, O., Colombat, P., Santini, G., Foulard, L. & Gorin, N.C. (1996) Purging of bone marrow in autologous bone marrow transplantation for non-Hodgkin's lymphoma: a case-matched comparison with unpurged cases by the European Blood and Marrow Transplant Lymphoma Registry. *Journal of Clinical Oncology*, **14**, 2454–2464.