Reduced intensity conditioning allogeneic stem cell transplantation for Hodgkin's lymphoma: identification of prognostic factors predicting outcome

Stephen P. Robinson,[1] Anna Sureda,[2] Carmen Canals,[3] Nigel Russell,[4] Dolores Caballero,[5] Andrea Bacigalupo,[6] Arturo Iriondo,[7] Gordon Cook,[8] Andrew Pettitt,[9] Gerard Socie,[10] Francesca Bonifazi,[11] Alberto Bosi,[12] Mauricette Michallet,[13] Effie Liakopoulou,[14] Johan Maertens,[15] Jakob Passweg,[16] Fiona Clarke,[17] Rodrigo Martino,[2] and Norbert Schmitz[18] on behalf of the Lymphoma Working Party of the EBMT

[1]BMT Unit, Bristol Children's Hospital, UK; [2]Clinical Hematology Division, Hospital Santa Creu i Sant Pau, Barcelona, Spain; [3]Lymphoma Working Party of the EBMT, Barcelona, Spain; [4]Department of Hematology, Nottingham City Hospital, UK; [5]Hematology Service, Hospital Clínico, Salamanca, Spain; [6]Department of Hematology, Ospedale San Martino, Genova, Italy; [7]Servicio Hematologia, Hospital U. Marques de Valdecilla, Santander, Spain; [8]Department of Hematology, St James's University Hospital, Leeds, UK; [9]Department of Hematology, Royal Liverpool University Hospital, UK; [10]Department of Hematology, Hôpital St. Louis, Paris, France; [11]Institute of Hematology and Medical Oncology, Bologna University, Italy; [12]Department of Hematology, Ospedale di Careggi, Firenze, Italy; [13]BMT Unit, Hôpital E. Herriot, Lyon, France; [14]Christie Hospital, Manchester, UK; [15]Department of Hematology, University Hospital Gasthuisberg, Leuven, Belgium; [16]Department of Internal Medicine, Hôpitaux Universitaires de Geneve, Geneva, Switzerland; [17]Department of Hematology, University of Birmingham, UK, and [18]Department of Hematology, AK-St Georg, Hamburg, Germany

ABSTRACT

Background

The role of reduced intensity conditioning allogeneic stem transplantation (RICalloSCT) in the management of patients with Hodgkin's lymphoma remains controversial.

Design and Methods

To further define its role we have conducted a retrospective analysis of 285 patients with HL who underwent a RICalloSCT in order to identify prognostic factors that predict outcome. Eighty percent of patients had undergone a prior autologous stem cell transplantation and 25% had refractory disease at transplant.

Results

Non-relapse mortality was associated with chemorefractory disease, poor performance status, age >45 and transplantation before 2002. For patients with no risk factors the 3-year non-relapse mortality rate was 12.5% compared to 46.2% for patients with 2 or more risk factors. The use of an unrelated donor had no adverse effect on the non-relapse mortality. Acute graft versus host disease (aGVHD) grades II-IV developed in 30% and chronic GVHD in 42%. The development of cGVHD was associated with a lower relapse rate. The disease progression rate at one and five years was 41% and 58.7% respectively and was associated with chemorefractory disease and extent of prior therapy. Donor lymphocyte infusions were administered to 64 patients for active disease of whom 32% showed a clinical response. Eight out of 18 patients receiving donor lymphocyte infusions alone had clinical responses. Progression-free and overall survival were both associated with performance status and disease status at transplant. Patients with neither risk factor had a 3-year PFS and overall survival of 42% and 56% respectively compared to 8% and 25% for patients with one or more risk factors. Relapse within six months of a prior autologous transplant was associated with a higher relapse rate and a lower progression-free.

Conclusions

This analysis identifies important clinical parameters that may be useful in predicting the outcome of RICaIICalloSCT in Hodgkin's lymphoma.

Key words: Hodgkin's lymphoma, allogeneic transplantation, prognosis.

Citation: Robinson SP, Sureda A, Canals C, Russell N, Caballero D, Bacigalupo A, Iriondo A, Cook G, Pettitt A, Socie G, Bonifazi F, Bosi A, Michallet M, Liakopoulou E, Maertens J, Passweg J, Clarke F, Martino R, and Schmitz N on behalf of the Lymphoma Working Party of the EBMT. Reduced intensity conditioning allogeneic stem cell transplantation for Hodgkin's lymphoma: identification of prognostic factors predicting outcome. Haematologica 2009;94:230-238. doi: 10.3324/haematol.13441

A list of contributing centers is available at: http://www.ebmt.org/5Working Parties/LWP/newstuds07/SRobinson_contributing_centres.pdf

Manuscript received June 3, 2008. Revised version arrived September 24, 2008. Manuscript accepted October 1, 2008.

Correspondence: Stephen Paul Robinson, BMT Unit, Bristol Children's Hospital, Upper Maudlin Street, Bristol BS2 8BJ, United Kingdom. E-mail: stephen.robinson@ubht.swest.nhs.uk

Introduction

Hodgkin's lymphoma (HL) remains a disease that is curable in the majority of patients using conventional chemoradiotherapy. However, some 20-30% of patients will either be refractory to initial therapy or relapse following front-line therapy. Many of these patients that fail initial therapy may be cured by high-dose therapy and autologous stem cell transplantation.[1-4] In contrast, high-dose therapy followed by allogeneic stem cell transplantation has been associated with substantial toxicity in patients with HL such that any benefit of reduced relapse rates is offset by the high transplant related mortality.[5-9] Consequently allogeneic stem cell transplantation is currently employed in a small fraction of patients with HL. In an attempt to reduce the toxicity of allogeneic stem cell transplantation the intensity of the conditioning regimen may be reduced, placing greater emphasis on the provision of a graft uncontaminated by tumor cells and the development of allogeneic graft versus malignancy reactions.[10,11] We have previously reported that RICalloSCT is associated with a lower non-relapse mortality (NRM) and an improved overall survival (OS) when compared to conventional alloSCT.[12] However, the reported experience of RICalloSCT in HL is limited[13-17] and its role in the management of HL remains to be clarified. We have, therefore, performed a retrospective analysis of 285 patients with HL who underwent a RIC alloSCT in an attempt to identify prognostic factors predicting the outcome.

Design and Methods

The EBMT is a voluntary organization comprising 525 transplant centers mainly from Europe. Member centers are required to submit minimal essential data (Med-A form) from consecutive patients to a central lymphoma registry. Participating transplant centers are subject to on-site audits to assess data accuracy and consecutive reporting. All centers that had submitted Med-A forms for patients with HL undergoing RIC alloSCT were invited to contribute additional data. Only patients over the age of 18 at the time of transplantation were included and patients undergoing planned tandem autologous transplants followed by RIC alloSCT were excluded. Minimum data required for the inclusion of a patient in the study were age, sex, histological diagnosis, date of diagnosis, details of prior high-dose therapy, disease status at transplantation, details of reduced intensity conditioning regimen, date of transplantation, donor relationship, date of follow-up, disease status at follow-up, date of disease progression or death and cause of death. Informed consent was obtained locally according to regulations applicable at the time of transplantation. After January 1, 2003, all EBMT centers have been required to obtain written informed consent prior to data registration.

Patients' characteristics

Between January 1995 and November 2005 153 centers reported 374 patients to the EBMT registry as having undergone reduced intensity allogeneic stem cell transplants for Hodgkin's disease. The minimum essential data required for entry to the study was available in 285 patients (from 110 centers) who form the study group described in this paper. The pre-transplant characteristics of these 285 patients are shown in Table 1. The patients with missing minimum essential data were analyzed as a separate group and compared to the study group of 285. There was no difference in pre-transplant characteristics, NRM, disease progression, progression-free survival (PFS) or OS between these two groups (*data not shown*).

Study definitions

RICalloSCT was defined according to published EBMT criteria[18] as follows: busulfan ≤8 mg/kg ± TBI ≤6 cGy (fractionated) ± purine analog± ATG; cyclophosphamide ≤60 mg/kg ± TBI≤≤6 cGy (fractionated) ± purine analog± ATG; TBI ≤6 cGy (fractionated) ± purine analog± ATG; melphalan 140 mg/m^2 + fludarabine; melphalan 70-140 mg/m^2 ± purine analogue ± campath 1H.

Status at transplantation was defined as follows: complete remission (CR), any CR; chemosensitive disease included all patients who had shown a response to the last therapy prior to transplantation with the exception of patients in CR [partial remission (PR), complete remission unconfirmed (CRu), VGPR and sensitive relapse/progression]; chemoresistant disease included all primary refractory and relapsed patients who had shown either no response or progressive disease following the last therapy prior to transplantation. Progression-free survival was measured in months as the time from the day of transplantation until disease relapse/progression or death from any cause. Both relapse and progression were defined as disease progression. Non-relapse mortality included all causes of death other than disease progression/relapse occurring at any time after RICalloSCT. T-cell depletion of the graft (TCD) includes all methods of TCD (CAMPATH *vs.* ATG *vs. in vitro* TCD) as individually each method had a similar impact on outcome (*data not shown*). Good performance status was defined as Karnofsky score >80% or ECOG score 0-1, whilst poor PS was defined as Karnofsky score <80% or ECOG score 2-3.

Statistical analysis

The probabilities of PFS and OS were calculated using the Kaplan-Meier product-limit estimate. The risk of acute and chronic graft versus host disease (GVHD), NRM and disease progression were calculated using cumulative incidence estimates, taking into account the competing risk structure. The following variables were studied for associations with outcomes by univariate analysis using the log-rank test for PFS and OS, and Cox univariate analysis for disease progression and NRM: year of RICalloSCT, age at diagnosis, age at transplant, sex, stage and B symptoms at diagnosis, number of prior lines of therapy, prior autologous transplant, time to relapse following autologous transplant, time from diagnosis to RICalloSCT, per-

formance status at transplant, disease status at transplant, donor type, stem cell source, T-cell depletion, donor/recipient sex, ABO compatibility, donor/recipient cytomegalovirus (CMV) status, type of RIC regimen. All factors showing a significant impact or a trend to an impact in the univariate analysis ($p<0.15$) and some additional variables of clinical interest were entered into the multivariate analysis. Multivariate analyses were performed using Cox proportional hazards regression using a stepwise conditional backward method. For some variables a separate category for missing data was created and studied in the analysis.[19] The proportional hazard assumption was tested for all variables in the selected models by introducing time as a (time-dependent) covariate and testing for a significant interaction with the risk factors under study. If a deviation from the proportionality assumption was found, a stratified Cox model was used. The final model was tested for interactions between variables. The influence of acute and chronic GVHD on relapse/progression was investigated using both a time-dependent Cox model and a landmark analysis. All statistical analyses were performed using SPSS version 13.0 (SPSS Inc.,Chicago, IL, USA) except for the cumulative incidence analyses that were performed with the NCSS97 (Number Cruncher Statistical System, Kaysville, UT, USA).

Table 1. Patient and donor and transplant details.

	N
Median age at diagnosis, years (range)	26.3 (14-57)
Median age at transplantation, years (range)	31.2 (18-57)
Age at transplant >45	32
Age at transplant <45	253
Male: Female	163:122
Stage at diagnosis, number (%)	
I	5 (2)
II	103 (36)
III	56 (20)
IV	72 (25)
NA	49 (17)
Diagnosis to transplantation, median months (range)	41 (4-332)
Median number of prior therapies (range)	4 (1-8)
Number of prior high-dose therapies (%)	
0	56 (20)
1	212 (74)
2	17 (6)
Median time from prior high-dose therapy to relapse, months (range)	9 (2-142)
Median time from prior high-dose therapy, months (range)	19 (4-146)
Disease status at transplantation (%)	
CR1	6 (2)
CR >=2	41 (14)
Chemosensitive	123 (43)
Chemoresistant	72 (25)
Untested relapse	43 (15)
Donor relationship, number (%)	
Matched sibling	172 (60)
Mismatched related	8 (3)
Matched unrelated	94 (33)
Mismatched unrelated	11 (4)
Donor sex match, number (%)	
Female to male	66 (23)
Other	209 (73)
NA	10 (4)
Stem cell source, number	
PBSC/BM	228/57
T-cell depletion, number	137
Conditioning Regimen, number (%)	
Fludarabine + Melphalan	137 (48)
Fludarabine + Busulphan	39 (14)
Fludarabine + Cyclophosphamide	30 (11)
Fludarabine + Cyclophosphamide + Thiotep	15 (5)
Other chemotherapy based RIC regimen	18 (6)
Low-dose TBI +/- Fludarabine	30 (11)
Low-dose TBI + other chemotherapy	16 (6)

Results

Conditioning regimens and transplantation details

A variety of different conditioning regimens were employed and are summarized in Table 1. The majority of patients (n=226, 79.5%) received conditioning with fludarabine based regimens whilst 46 (16%) received low-dose TBI based regimens. T-cell depletion of the graft was performed in 137 (48.1%) transplants, the majority by *in vivo* T-cell depletion using either ATG (n=80) or CAMPATH (n=59) whilst 10 patients received an *in vitro* T-cell depleted graft. Post-transplantation GVHD prophylaxis was achieved using cyclosporin alone, cyclosporin and methotrexate, cyclosporin and mycophenolate mofetil in 86 (32%), 120 (45%) and 48 (18%) cases respectively.

Engraftment and chimerism studies

Of 285 patients, 272 were evaluable for engraftment of whom 270 (99%) engrafted and 2 (1%) did not. Four patients initially engrafting subsequently rejected their graft. The median times to neutrophil and platelet engraftment (platelets >50) were 14 days (range 0-74) and 15 days (range 0-373) respectively. Neutrophil and platelet engraftment was significantly delayed in patients receiving BM when compared to PBSC. Chimerism analysis was available in 212 patients of whom 175 (83%) were fully donor and 37 were mixed donor-recipient (17%) within the first 100 days following transplant.

Non-relapse mortality

Sixty patients died of non-relapse mortality at a median of 91 days (range 1 day-20 months) following transplantation. The causes of death included infection (n=24), GVHD and infection (n=10), GVHD alone (n=7), pulmonary toxicity (n=6), multi-organ failure (n=2), post-transplant lymphoproliferative disease (n=2), TTP (n=2), and miscellaneous other causes (n=7). The cumu-

lative incidence estimate of non-relapse mortality at 100 days, one year and three years post-transplant were 10.9%, 19.5% and 21.1% respectively (Figure 1A). In multivariate analysis NRM was associated with poor performance status, chemorefractory disease at transplantation, age greater than 45 and transplantation before 2002 (Table 2). Identifying poor PS, chemorefractory disease and older age as adverse risk factors for NRM, patients with no adverse risk factors had a 3-year NRM rate of 12.5% compared with 46.2% for those with 2 or 3 risk factors (Figure 1B). The use of an unrelated donor and a single prior high-dose procedure had no impact on the NRM.

Graft versus host disease

In the 279 patients at risk 138 (49%) developed acute GVHD, 132 (47%) did not develop this complication and in 9 (3%) data was unavailable. Acute GVHD grades I, II, III and IV developed in 57 (20%), 47 (17%), 25 (9%) and 8 (3%) patients respectively. The CI of grade II-IV acute GVHD at 100 days was 30% and was associated with T-replete transplants, an interval from diagnosis to transplant of >48 months, male recipients of female donors and two prior high-dose procedures. Patients developing grade II-IV aGVHD had a significantly higher NRM (RR, 2.9; CI1.7-5.1; $p<0.001$), a lower PFS (RR, 1.5; CI 1.1-2.0; $p=0.007$) and OS (RR, 1.7; CI 1.2-2.4; $p=0.001$) but their risk of disease relapse was not reduced. Two hundred and twenty-six patients survived beyond 100 days and were evaluable for chronic GVHD of whom 126 (56%) remained free of cGVHD, 87 (38%) developed cGVHD and in 13 (5%) data was not available. Of those developing cGVHD, 42 (19%) developed limited and 42 (19%) extensive cGVHD and in 3 the extent was not reported. The cumulative inci-

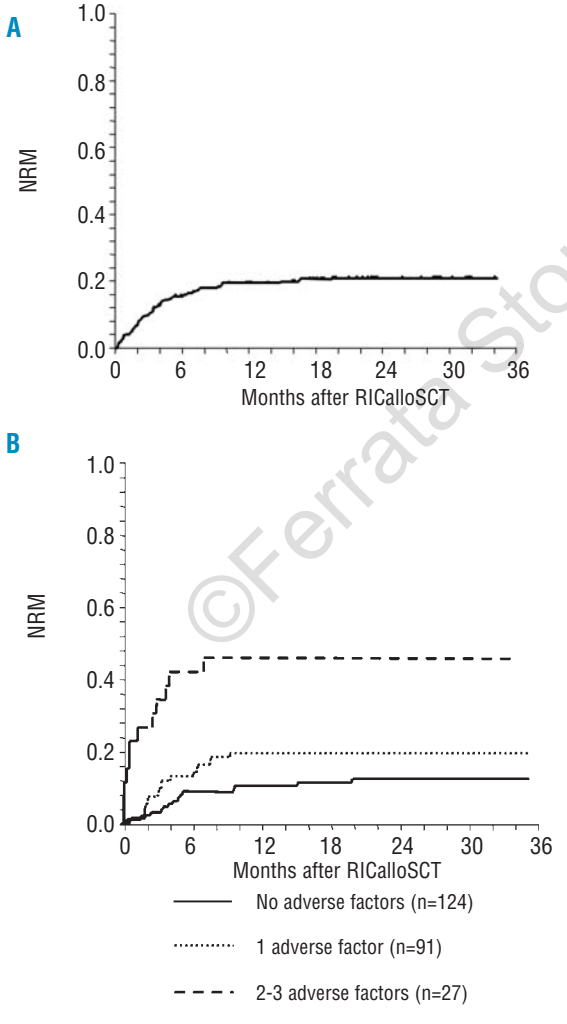

Figure 1. (A) Cumulative incidence estimate of non-relapse mortality (NRM) for 285 patients. (B) The impact of risk factors on NRM. Good risk: age <45, good performance status and chemosensitive disease. Poor risk: age >45, poor performance status and chemorefractory disease.

Table 2. Multivariate analysis.

Outcome	Relative risk	Confidence interval	p
NRM			
Disease status at transplant			
CR	1.0	–	
Refractory	2.6	1.5-4.5	0.001
Age at transplant			
<45	1.0	–	
>45	2.4	1.1-5.0	0.025
Performance status			
Good	1.0	–	
Poor	3.9	1.8-8.3	<0.001
Date of RICalloSCT			
After 2002	1.0	-	
Pre-2002	1.7	1.0-2.9	0.05
Disease progression			
Disease status at transplant			
CR	1.0	–	
Refractory	2.1	1.5-2.9	<0.001
Prior therapy			
<3 lines	1.0	–	
>3 lines	1.7	1.2-2.5	0.005
Sex match			
Other	1.0	–	
Donor Female/Rec Male	1.5	1.0-2.2	0.04
OS			
Disease status at transplant			
CR	1.0	–	
Refractory	1.8	1.3-2.5	<0.001
Performance status			
Good	1.0	–	
Poor	2.4	1.4-4.1	0.001
Sex match			
Other	1.0	–	
Donor Female/Rec Male	1.5	1.0-2.1	0.034
PFS			
Disease status at transplant			
CR	1.0	-	
Refractory	2.2	1.6-2.9	<0.001
Performance status			
Good	1.0	-	
Poor	1.9	1.2-3.0	0.009
Donor/recipient sex			
Other	1.0	-	
Donor F/recipient M	1.4	1.0-1.9	0.035

dence estimate of cGVHD at three years post-transplant was 42% (Figure 2A). There was a non-significant trend to a higher incidence of chronic GVHD in recipients of T-replete transplants, mismatched transplants and sex mismatched male recipients. In a Cox regression model the development of chronic GVHD was associated with a higher NRM (RR, 3.0; CI 1.3-7.1) and a trend to lower relapse rate (*data not shown*) but had no impact on PFS or OS. In a landmark analysis the development of chronic GVHD by nine months post-transplant was associated with a significantly lower relapse rate (RR,2.3; CI 1.2-4.4; p=0.008) (Figure 2B).

Response to transplantation

The disease status at day 100 post-transplant was reported in 238 out of 257 evaluable patients. Overall 123 (48%) patients were in CR and 66 (26%) were not in CR and 49 (19%) had progressive disease. Of the 47 patients in CR at the time of transplantation, 41 remained in CR (87%) and 6 (13%) progressed. Of the 104 patients with chemosensitive disease, 58 (56%) achieved a CR, 24 (23%) had a PR or stable disease and 16 (15%) had progressive disease. Of the 87 patients with chemorefractory disease or untested relapse at transplantation 24 achieved a CR (28%), 26 had a PR or stable disease (30%) and 27 (31%) had progressive disease.

Disease relapse and progression

Following transplantation 147 patients have relapsed or progressed at a median time of 6.3 months (range 1-59 months) post-transplant. The cumulative incidence estimate of disease progression at one, three and five years was 41%, 53% and 59% respectively (Figure 3A). In multivariate analysis chemorefractory disease, more than 3 lines of prior therapy and male recipients of female donors were associated with a significantly higher relapse rate (Table 2). Patients with none of these risk

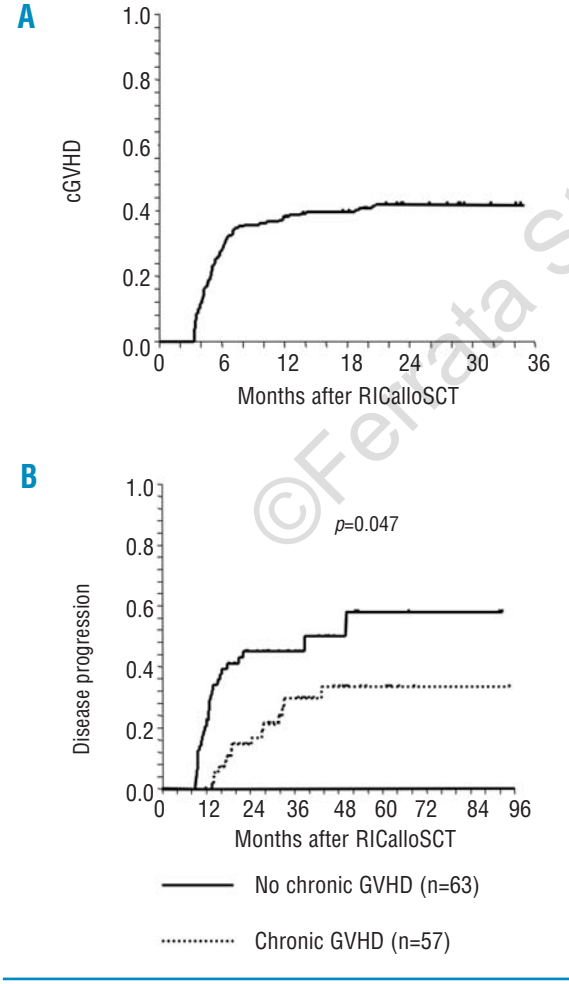

Figure 2. (A) Cumulative incidence estimate of chronic GVHD. (B) Impact of chronic GVHD by 9 months post-transplant on the disease progression rate.

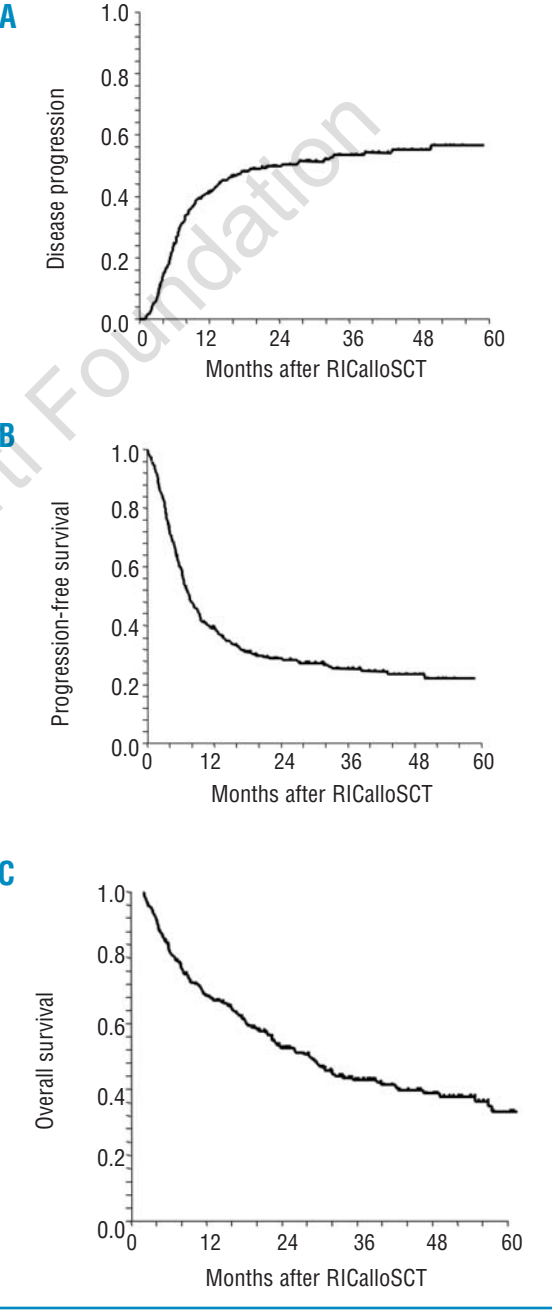

Figure 3. (A) Cumulative incidence estimate of disease progression. Kaplan-Meier estimates of (B) progression-free survival and (C) overall survival.

factors present had a 3-year disease progression rate of 46.8% compared with 70.2% for patients with 2 or 3 of these factors present.

Overall survival and progression-free survival

With a median follow-up of 26 months (range 3-94 months) 126 patients remain alive and 159 have died. The Kaplan-Meier estimates of OS and PFS at one, two and three years were 67% and 52%, 43% and 39%, 29% and 25% respectively (Figure 3B and 3C). In multivariate analysis patients in CR or with chemosensitive disease, those with a good performance status, transplants other than sex mismatched male recipients and CMV -/- transplants had a significantly better OS (Table 2). For PFS good performance status, CR or chemosensitive disease at transplantation and transplants other than male recipients from female donors were associated with a significantly better PFS in the multivariate analysis (Table 2). Older patient age, use of an unrelated donor and more than 3 lines of prior therapy, did not negatively impact on the PFS or OS. Identifying chemorefractory disease and poor performance status as risk factors for a poor OS and PFS patients with neither of these risk factors have a 3-year PFS and OS of 42% and 56% compared to 8% and 25% for patients with 1 or 2 of these risk factors (Figure 4A and 4B). In an analysis restricted to patients who had relapsed after a prior autologous transplant, relapse within six months of the autograft was associated with a significantly worse disease progression rate (RR=1.9 (1.2- 3.1) p=0.01) and PFS (RR=1.9 (1.2- 2.9) p=0.003) following the RICalloSCT.

Donor lymphocyte infusions

Donor lymphocyte infusions (DLI) were given to 79 patients at a median of six months (range 1-38) post-transplant, 64 for the treatment of persistent or progressive disease and 13 for either mixed chimerism or as part of a pre-emptive strategy to prevent relapse. The median dose of DLI administered was 1×10^6 $CD3^+$/kg (range $0.2\text{-}7.6\times10^6$). Overall 52% of patients developed GVHD following DLI and the Kaplan-Meier estimate of median OS following DLI was 20 months. Disease responses were available in 41 patients of whom 22 (54%) showed no response, 13 (32%) achieved a CR or PR, 4 (10%) had a brief clinical response and 2 (5%) had stable disease at last assessment. DLIs were administered to 18 patients without any additional therapy in whom 8 (44%) had a response, one had stable disease, 8 failed to respond and 2 were not evaluated.

Discussion

In this analysis we have described the largest series of RICalloSCT for HL reported to date and have identified important clinical parameters predicting transplant outcomes. Whilst registry based retrospective analyses allow the study of large numbers of patients and the identification of clinical parameters that influence outcome there are also inherent weaknesses with such studies. Only patients who undergo transplantation are reported to the registry and therefore represent a selected population. Data submission from centers may not be complete despite the requirement for consecutive case reporting, the provision of minimal essential data and on-site audits. Despite these limitations, this study provides clinically relevant data that may help guide physicians in managing individual patients.

The patients in this study represent a heavily pretreated group where 80% had undergone previous high-dose therapy and 40% of patients had either chemorefractory disease or untested relapse at the time of transplant. Forty-two percent received transplants from mismatched or unrelated donors. Despite this risk profile, the NRM was 11% at 100 days and 21% at three years and similar to that reported in other studies of RICalloSCT in HL.[13-17] For younger patients with a good PS and chemosensitive disease the total NRM was 12%. These results compare favorably with a NRM of 43-61% reported after conventional conditioning regimens[5-9] over the preceding two decades. The lower NRM rates

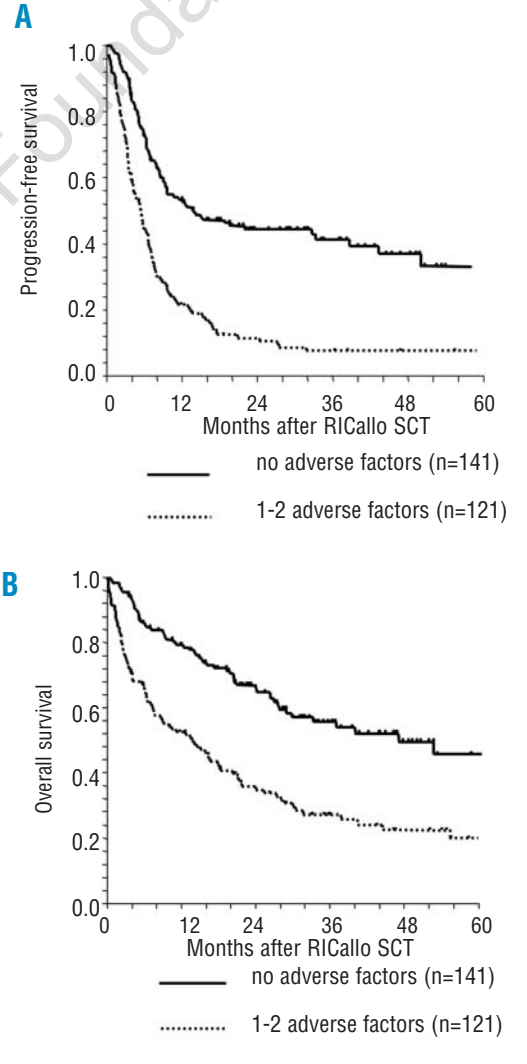

Figure 4. (A) **The impact of risk factors on (A) progression-free survival and (B) overall survival. Good risk: chemosensitive disease, good PS. Poor risk: chemorefractory disease, poor PS.**

observed after RICalloSCT for HL may relate in part to improvements in tissue typing and supportive care. However, patients undergoing conventional alloSCT over the same period still have a substantially greater NRM.[12] The NRM was significantly greater in patients with chemorefractory disease, older age or a poor performance status.

The identification of these risk factors may help to guide physicians in the choice of therapy for individual patients. It is noteworthy, that for patients receiving a transplant from a matched unrelated donor and for patients who had undergone a single previous high-dose procedure the NRM was not adversely affected. Therefore, lack of a sibling donor and a single prior high-dose procedure should not prevent consideration of an RICalloSCT.[20,21] We were not able to demonstrate in this study that any of the RIC regimens were associated with a higher NRM although there was a non-significant trend to a higher NRM in patients receiving non-TBI based conditioning.

Disease progression was the major cause of treatment failure following RICalloSCT with 59% of patients relapsing by five years after the transplant. This compares with rates of 43-55% in other series of RICalloSCT in HL[14-16] and 48-65% following conventional allogeneic transplantation.[5-9] Patients who received fewer lines of prior therapy and those in CR had a significantly lower disease progression rate. If RICalloSCT were performed earlier in the disease course lower disease progression rates may be anticipated. However, for patients with refractory disease at the time of RICalloSCT the risk of subsequent relapse is substantial and alternative strategies should be considered. It remains to be established if any of the RIC regimens is superior in terms of reducing the relapse rate. The Seattle group have reported relapse rates of 47% at one year following low-dose TBI±fludarabine.[16] Conversely, more intensive conditioning with BEAM or planned tandem autografts/RICallografts may be associated with a lower relapse rate.[22-24] Given that the overall NRM of the various RIC regimens in this and other studies is similar,[14-17] the more intensive regimens may be more effective in controlling HL without increasing toxicity. However, prospective controlled studies will be required to confirm the superiority of any one regimen.

Historically, the evidence for a graft versus HL effect has been limited to the indirect observations that lower relapse rates were observed in patients developing GVHD[7] and that relapse rates were lower after allogeneic transplantation when compared to autologous transplantation.[9,25] In this study, the development of chronic GVHD was associated with a lower relapse rate whilst acute GVHD had no impact on the relapse rate. The most direct evidence for a graft versus HL effect comes from observations relating to disease responses to DLI[14,15,17] which were observed in 32% of patients receiving DLI in the current study. However, the efficacy of DLI is likely to depend upon the bulk of disease at the time of administration and the optimal use of DLI requires further refinement. Pre-emptive dose escalating or PET scan guided strategies may improve the overall efficacy of DLIs.[26,27] As previously reported, we observed no impact of T-cell depletion upon the rates of disease progression despite being associated with a lower incidence of acute GVHD.[28,29] The role of T-cell depletion and the need for subsequent DLI post-RICalloSCT requires further study in prospective comparative studies.

As a consequence of the high relapse rate, the PFS and OS for the patients in this study was disappointingly low and only marginally better than that reported following conventional allogeneic SCT.[5-8] In several other reports of RICalloSCT in HL, the PFS has ranged from 18% at one year to 32% at four years.[14,15] Patients with a good performance status, in CR or with chemosensitive disease at the time of transplantation had significantly better PFS and OS estimates. The low PFS and OS rates observed in this cohort may relate to the late stage of disease at which the RICalloSCTs were performed. Eighty percent of patients in this study had relapsed after an autologous SCT at a median of nine months. Early relapse after an autologous transplant is associated with a poor prognosis[30] and we found that relapse within six months of an autologous SCT was predictive of outcome after the RICalloSCT.

However, the data presented in this study suggest that RICalloSCT may be an effective salvage strategy for the minority of patients with good risk features who relapse after an autologous SCT,[31] and that outcomes are similar for both sibling and MUD transplants. Conversely for patients with chemorefractory disease or a poor performance status, the overall outcome is poor and it is difficult to recommend RICalloSCT for these patients.

Employing RICalloSCT earlier in the course of HL remains controversial. The standard salvage therapy for patients with refractory or relapsing disease is high-dose therapy followed by an autologous stem cell transplant.[1,2] However, for subgroups of patients with poor risk features autologous transplants are less successful[3,20,32,33] and there is growing concern regarding the late risk of secondary MDS/AML following autologous transplants.[34,35] For patients deemed to be at high risk of failing an autologous transplant a RICalloSCT may represent a more effective therapy and prospective comparative studies in this setting should be considered.

Authorship and Disclosures

SPR designed the study, directed the statistical anlysis and wrote the manuscript; AS and NS helped design the study and contributed to the manuscript; CC conducted data collection and statistical analysis. The following authors contributed data to the study and contributed significantly to the writing of the manuscript; NG, SPR designed the study, directed the statistical anlysis and wrote the manuscript; AS and NS helped design the study and contributed to the manuscript; CC conducted data collection and statistical analysis.

The following authors contributed data to the study and contributed significantly to the writing of the manuscript: NR, DC, AB, AI, GC, AP, GS, FB, AB, MM, EL, JM, JP, FC, RD.

The authors reported no potential conflicts of interest.

References

1. Linch DC, Winfield D, Goldstone AH, Moir D, Hancock B, McMillan A, et al. Dose intensification with autologous bone-marrow transplantation in relapsed and resistant Hodgkin's disease: results of a BNLI randomised trial. Lancet 1993;341: 1050-4.
2. Schmitz N, Pfistner B, Sextro M, Sieber M, Carella AM, Haenel M, et al. Aggressive conventional chemotherapy compared with high dose chemotherapy with autologous haematopoietic stem cell transplantation for relapsed chemosensitive Hodgkin's disease: a randomised trial. Lancet 2002; 359:2065-71.
3. Sureda A, Arranz R, Iriondo A, Carreras E, Lahuerta JJ, García-Conde J, et al. Autologous stem cell transplantation for Hodgkin's disease: results and prognostic factors in 494 patients from the Grupo Espanol de Linfomas/Transplante Autologo de Medula Osea Spanish Cooperative Group. J Clin Oncol 2001;19:1395-404.
4. Sweetenham JW, Carella AM, Taghipou G, Cunningham D, Marcus R, Della Volpe A, et al. High-dose therapy and autologous stem-cell transplantation for adult patients with Hodgkin's disease who do not enter remission after induction chemotherapy: results in 175 patients reported to the European Group for Blood and Marrow Transplantation. J Clin Oncol 1999;17:3101-9.
5. Gajewski JL, Phillips GL, Sobocinski KA, Armitage JO, Gale RP, Champlin RE, et al. Bone marrow transplants from HLA-identical siblings in advanced Hodgkin's disease. J Clin Oncol 1996;14:572-8.
6. Akpek G, Ambinder RF, Piantidoosi S, Abrams RA, Brodsky RA, Vogelsang GB, et al. Long term results of blood and marrow transplantation for Hodgkin's lymphoma. J Clin Oncol 2001;19:4314-21.
7. Milpied N, Fielding AK, Pearce RM, Ernst P, Goldstone AH. Allogeneic bone marrow transplant is not better than autologous transplant for patients with relapsed Hogkin's disease. J Clin Oncol 1996;14:291-6.
8. Anderson JE, Litzow MR, Appelbaum FR, Schoch G, Fisher LD, Buckner CD, et al. Allogeneic, syngeneic and autologous transplanation for Hodgkin's disease: the 21-year Seattle experience. J Clin Oncol 1993;11:2342-50.
9. Peniket AJ, Ruiz de Elvira MC, Taghipour G, et al. Allogeneic transplantation for lymphoma produces a lower relapse rate than autologous transplantation but survival is worse because of higher treatment related mortality-a report of 764 cases from the EBMT lymphoma registry. Blood 90:1997 Suppl; abstract 255a].
10. Slavin S, Nagler A, Naparstek E, Kapelushnik Y, Aker M, Cividalli G, et al. Nonmyeloablative stem cell transplantation and cell therapy as an alternative to conventional bone marrow transplantation with lethal cytoreduction for the treatment of malignant and nonmalignant hematologic diseases. Blood 1998;91: 756-63.
11. Khouri IF, Keating M, Korbling M, Przepiorka D, Anderlini P, O'Brien S, et al. Transplant-lite: induction of graft-versus-malignancy using fludarabine-based nonablative chemotherapy and allogeneic blood progenitor cell transplantation as treatment for lymphoid malignancies. J Clin Oncol 1998;16:2817-24.
12. Sureda A, Robinson SP, Canals C, Carella AM, Boogaerts MA, Caballero D, et al. Reduced-intensity conditioning compared with conventional allogeneic stem-cell transplantation in relapsed or refractory Hodgkin's lymphoma: an analysis from the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. J Clin Oncol 2008; 26:455-62.
13. Robinson SP, Goldstone AH, Mackinnon S, Carella A, Russell N, de Elvira CR, et al. 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 2002;100: 4310-6.
14. Anderlini P, Saliba R, Acholonu S, G-J Okoroji, M Donato, S Giralt, et al. Reduced-intensity allogeneic stem cell transplantation in relapsed and refractory Hodgkin's disease: low transplant-related mortality and impact of intensity of conditioning regimen. Bone Marrow Transplant 2005;35:943-51.
15. Peggs KS, Hunter A, Chopra R, Parker A, Mahendra P, Milligan D, et al. Clinical evidence of a graft-versus lymphoma effect after reduced intensity allogeneic transplantation. Lancet 2005;365:1906-8.
16. Burroughs LM, Maris MB, Sandmaier BM, et al. HLA-matched related or unrelated donor nonmyeloablative conditioning and hematopoietic cell transplant for patients with advanced Hodgkin's lymphoma. Biol Blood Marrow Transplant 2004:10:73 [Abstract].
17. Alvarez I, Sureda A, Caballero, Urbano-Ispizua A, Ribera JM, Canales M, et al. Non-myeloablative stem cell transplantation is an effective therapy for refractory or relapsed Hodgkin's lymphoma: results of a Spanish Prospective Cooperative Protocol. Biol Blood Marrow Transplant 2006;12:172-83.
18. European Bone Marrow Transplant Registry. Operational manual. http://www.ebmt.org/4Registry/Registry docs/MEDAB%20Manual.pdf
19. Klein JP, Rizzo JD, Zhang M-J, Keiding N. Statistical methods for the analysis and presentation of the results of bone marrow transplantats. Part 2: Regression modelling. Bone Marrow Transplant 2001;28: 1001-11.
20. Branson K, Chopra R Kottaridis P, McQuaker G, Parker A, Schey S, et al. Role of Nonmyeloablative allogeneic stem-cell transplantation after failure of autologous transplantation in patients with lymphoproliferative malignancies. J Clin Oncol 2002;20:4022-31.
21. Chakraverty R, Peggs K, Chopra R, Milligan DW, Kottaridis PD, Verfuerth S, et al. Limiting transplantation-related mortality following unrelated donor stem cell transplantation by using a nonmyeloablative conditioning regimen. Blood 2002;99:1071-8.
22. Carella AM, Cavaliere M, Lerma E, Ferrara R, Tedeschi L, Romanelliet A, et al. Autografting followed by nonmyeloablative immunosuppressive chemotherapy and allogeneic stem-cell transplantation as treatment of resistant Hodgkin's disease and non-Hodgkin's lymphoma. J Clin Oncol 2000;18:3918-24.
23. Das-Gupta E, Byrne JL, Craddock C, Robinson SP, Devereux S, Pagliuca A, et al. Reduced intensity allogeneic transplantation using BEAM-alemtuzumab in patients with lymphoid malignancy: long term results and impact of intervention with DLI (abstract). Blood 2005;106:suppl[Abstract 2890a].
24. Faulkner RD, Craddock C, Byrne JL, Mahendra P, Haynes AP, Prentice HG, et al. BEAM-alemtuzumab reduced-intensity allogeneic stem cell transplantation for lymphoproliferative diseases: GVHD, toxicity, and survival in 65 patients Blood 2004;103:428-34.
25. Jones RJ, Ambinder RF, Piantadosi S, Santos GW. Evidence of a graft-versus-lymphoma effect associated with allogeneic bone marrow transplantation. Blood 1991;77: 649-53.
26. Hart DP, Avivi I, Thomson KJ, Peggs KS, Morris EC, Goldstone AH, et al. Use of ^{18}F-FDG positron emission tomography following allogeneic transplantation to guide adoptive immunotherapy with donor lymphocyte infusions. Br J Haematol 2005;128:824-9.
27. Peggs KS, Thomson KJ, Hart DP, Geary J, Morris EC, Yong K, et al. Dose-escalated donor lymphocyte infusions following reduced intensity transplantation: toxicity, chimerism, and disease responses. Blood 2004;1031548-56.
28. Perez-Simon JA, Kottaridis PD, Martino R, Craddock C, Caballero D, Chopra R, et al. Nonmyeloablative transplantation with or

without alemtuzumab: comparison between 2 prospective studies in patients with lymphoproliferaive disorders. Blood 2002; 100:3121-7.
29. Peggs KS, Sureda A, Qian W, Caballero MD, Hunter A, Urbano-Ispizua A, et al. Reduced-intensity conditioning for allogeneic haematopoietic stem cell transplantation in relapsed and refractory Hodgkin lymphoma: impact of alemtuzumab and donor lymphocyte infusions on long-term outcomes. Br J Haematol 2007;139:70-80.
30. Horning S, Fanale M, deVos S, Borchman P, Illidge T, Engert A, et al. Defining a population of Hodgkin lymphoma patients for novel therapeutics: an international effort. Ann Oncol 2008;19:Suppl 4[Abstract 118].
31. Thomson KJ, Peggs KS, Smith P, Chopra R, Cavet J, Hunter A, et al. Improved outcome following reduced intensity allogeneic transplantation in Hodgkin's lymphoma relapsing post-autologous transplantation. Bone Marrow Transplant 2008;41:765-70.
32. Hahn T, Benekli M, Wong C, Moysich KB, Hyland A, Michalek AM, et al. A prognostic model for prolonged event-free survival after autologous or allogeneic blood or marrow transplantation for relapsed and refractory Hodgkin's disease. Bone Marrow Transplant 2005;35: 557-66.
33. Popat U, Hosing C, Saliba, Anderlini P, van Besien K, Przepiorka D, et al. Prognostic factors for disease progresión alter high-dose chemotherapy and autologous hematopoietic ítem cell transplantation for recurrent or refractory Hodgkin's lymphoma. Bone Marrow Transplant 2004;33:1015-23.
34. Brown J, Yeckes H, Friedberg JW, Neuberg D, Kim H, Nadler LM, et al. Increasing incidence of late second malignancies after conditioning with cyclophosphamide and total-body irradiation and autologous bone marrow transplantation for Non-Hodgkin's lymphoma. J Clin Oncol 2005;22:2208-14.
35. Bhatia S, Robison LL, Francisco, Carter A, Liu Y, Grant M, et al. Late mortality in survivors of autologous hematopoietic-cell transplantation: report from the Bone Marrow Transplant Survivor Study. Blood 2005;105:4215-22.