Autologous blood stem cell transplantation for Hodgkin and non-Hodgkin lymphoma: Complications and outcome

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ABSTRACT

Background. We analysed data on patients of Hodgkin and non-Hodgkin lymphoma treated with high dose chemotherapy followed by autologous stem cell transplantation to determine the toxicity, pattern of infections and long term outcome.

Methods. There were 34 male and 10 female patients (median age 35 years, range 15–67 years). Before transplantation, 31 patients (70.5%) had chemosensitive disease and 13 (29.5%) had chemoresistant disease. Granulocyte-colony stimulating factor mobilized peripheral blood stem cells were used as the source of stem cells. The patients received high dose chemotherapy using CBV (cyclophosphamide, BCNU and VP-16 [etoposide] $n=38$), BEAM (BCNU, etoposide, cytosine arabinoside and melphalan, $n=3$), cytosine arabinoside, etoposide and melphalan ($n=2$) and melphalan alone ($n=1$). Prophylaxis with antifungal drugs (fluconazole/itraconazole) and acyclovir was used.

Results. Following transplant, 32 patients (72.7%) responded; complete response was achieved in 25 patients (56.8%) and partial response in 7 (15.9%). The rate of complete response was higher for patients with pre-transplant chemosensitive disease (23/31 [74.2%] *v.* 2/13 [15.4%], $p<0.001$). Gastrointestinal toxicity, and renal and liver dysfunctions were major non-haematological toxicities; 3 patients (7%) died of regimen-related toxicity. Infections (predominantly Gram-negative) accounted for 2 deaths (4.5%) seen before day 30. At a median follow up of 79 months (range 14–168 months), median overall and event-free survival were 78 months and 28 months, respectively. Estimated mean (SE) overall and event-free survival at 60 months were 54.34% (0.07) and 34.3% (9.88), respectively.

Conclusion. Patients with pre-transplant chemosensitive disease and those who achieved complete response following transplant had a significantly better chance of survival.

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INTRODUCTION

High dose chemotherapy (HDCT) followed by autologous haemopoietic stem cell transplantation (ASCT) is the standard treatment for chemosensitive relapsed Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). Infections and non-haematological toxicities are common complications seen in the early post-transplant period (0–30 days) and are primarily related to HDCT. Relapse and secondary malignancy are late complications.[1] While results of ASCT have been reported from many centres in the West,[2–5] such data are not readily available from India.[6,7] We analysed our results in patients with HL and NHL who underwent ASCT.

METHODS

A total of 44 patients with HL and NHL underwent ASCT till December 2008. The patients' median age was 35 years (range 15–67 years). Before transplant, 31 patients (70.5%) had chemosensitive disease while 13 (29.5%) had chemorefractory or chemoresistant disease; including 3 patients with stable disease (Table I).

Transplant protocol

All patients were evaluated thoroughly on an outpatient basis before transplant. This included history, physical examination and details of prior treatment. Investigations including haemogram, renal and liver function tests, bone marrow biopsy, echocardiography or multi-gated acquisition (MUGA) scan, pulmonary function tests and viral markers were done to assess overall fitness before ASCT. Patients were explained about the procedure, potential risks and benefits. A central line (Hickman catheter) was inserted. Written informed consent was obtained before treatment.

Procedure

Mobilized peripheral blood stem cells (PBSCs) were harvested for all the patients. They received granulocyte-colony stimulating factor (G-CSF) 5 μg/kg twice daily subcutaneously for 6 days to mobilize PBSCs. Stem cells were harvested on days 5 and 7 using Hemonetics cell separator-MCS 3p (Hemonetics, Braintree, MA, USA). PBSC harvest was done from the median cubital vein in 40 patients, and from a central line (subclavian or internal jugular vein) in 4 patients. A mean of 2 harvests were done per patient (range 1–4). Mononuclear cells (MNCs) were counted manually by doing a differential count on the stem cell preparation. For CD34 count, cells were labelled with fluorescein-conjugated anti-CD34 and analysed using a FACS scan flow cytometer to yield absolute CD34+ counts.[7,8] Stem cells were cryopreserved at

TABLE I. Patients' characteristics (*n*=44)

Characteristic	Value
Median age (range)	35 (15–67) years
Male:female	34:10
Diagnosis	
Hodgkin lymphoma	25 (56.8)
Non-Hodgkin lymphoma	19 (43.2)
Preparative regimen	
Carmustine, etoposide, cyclophosphamide	38
Carmustine, etoposide, cytosine arabinoside, melphalan	3
Melphalan, cytosine arabinoside and etoposide	2
Melphalan alone	1
Status at the time of transplant	
Chemosensitive disease	
Partial response 1	6 (13.6)
Complete response 2	10 (22.7)
Partial response 2	15 (34.1)
Chemoresistant/refractory disease (stable 3)	13 (29.5)
WHO performance status	
0	8 (18.2)
1	20 (45.5)
2	9 (20.5)
3	7 (15.9)
Response to transplant	
Complete response	25 (56.8)
Partial response	7 (15.9)
Stable disease	4 (9.1)
Progressive disease	3 (6.8)
Died	5 (11.4)

Values in parentheses are percentages

–80 °C using cryoprotectant mixture consisting of 7.5% dimethyl sulphoxide (DMSO), albumin and saline.[9] The viability of stem cells was assessed by the trypan blue dye test.

High dose chemotherapy

For HL and NHL, carmustine (BCNU), cyclophosphamide and etoposide (VP-16) were given to 38 patients (CBV); BCNU, cytosine arabinoside, VP-16 and melphalan (BEAM) were given to 3; cytosine arabinoside, VP-16 and melphalan to 2 and melphalan alone to 1 patient. HDCT was administered as per standard guidelines; patients were monitored round the clock for any potential toxicity. Autologous stem cells were re-infused intravenously on day 0 through a central venous catheter preceded by i.v. pheniramine maleate 50 mg. Post-transplant, patients received G-CSF 5 µg/kg daily subcutaneously until engraftment. All blood products transfused during the post-transplant period were irradiated with 25 Gy.

Antimicrobial prophylaxis and febrile neutropenia

Patients were admitted in a single room without laminar airflow or HEPA filter; reverse barrier nursing was practised. All patients received prophylaxis against fungal infections, with fluconazole till 1998 and later with itraconazole.[10] Ciprofloxacin was used for antibacterial and acyclovir for antiviral prophylaxis. Patients were advised to avoid raw, uncooked food over the next 4 weeks. If a patient was febrile (temperature ≥101°F), a careful clinical evaluation was done followed by a chest X-ray and blood was sent for culture. They were then started on a combination of a third-generation cephalosporin and aminoglycoside or double β-lactams (for those with renal dysfunction). Antibiotics were modified based on the culture reports. For patients with persistent fever, vancomycin and amphotericin-B were added on days 3, 4 and 5, respectively.[7]

Toxicity

All non-haematological dysfunction was considered 'regimen-related' unless they could be explained by another cause. A grading scale described by Bearman *et al*.[11] was used for toxic complications of transplant: grade 0 represented no toxicity, grade I toxicity was fully reversible without specific intervention; grade II toxicity was not life-threatening, but required specific measures to be reverted; grade III was life-threatening but reversible; and grade IV toxicity was fatal.

Follow up

Patients were evaluated for response as per the WHO criteria,[13] 4 weeks after transplant on an outpatient basis. During follow up patients were seen every 2–3 months for the first 2 years and then every 6 months. The median follow up for the whole group was 79 months (range 14–168 months). The data were censored on 31 December 2009.

Statistical analysis

An intention-to-treat analysis was done. The prognostic factors for response to transplant were analysed by Pearson chi-square test. All survival times were calculated from the date of transplant. Overall survival (OS) was defined as the time from date of transplant until death or date of censor. Event-free survival (EFS) was calculated from the date of transplant to disease progression or death (regardless of cause of death). Curves for OS and EFS were plotted according to the method of Kaplan and Meier and were compared by the log rank test. Statistical analysis was done with the SPSS software (version 11.5).

RESULTS

Engraftment

The mean number of mononuclear and CD 34+ cells transfused was 4.67×10^8/kg (range $1.22–9.0\times10^8$/kg) and 2.42×10^6/kg (range $0.21–7.97\times10^6$/kg), respectively. Stem cells viability (after thawing) ranged from 88% to 98%.

Haematological recovery

The median time to engraftment (absolute neutrophil count ≥500/cmm for 3 consecutive days) was 11 days (range 9–21 days) and median time to platelet transfusion independence was 12 days (range 8–19 days). Following transplant, patients received a mean of 2 units of red cells and 3 units of single donor platelet transfusion. Post-transplant patients received G-CSF for a median of 12 days (range 9–21 days).

Response to transplant

Thirty-two of 44 patients (72.7%) responded; complete response (CR) in 25 (56.8%), and partial response (PR) in 7 (15.9%). Four patients (9.1%) had stable disease and 3 patients (6.8%) had either no response or progressed (Table I). Among 31 patients with pre-transplant chemosensitive disease, 23 (74.2%) achieved CR compared with 2 of 13 patients (15.4%) with chemorefractory/resistant disease ($p<0.001$; Table II).

HL. The overall response rate was 88%; CR in 17 (68%) and PR 5 (20%). The CR rate was higher among patients who had chemosensitive disease compared with chemoresistant disease (84.4% [16/19] *v.* 16.6% [1/6]).

NHL. This group was heterogeneous in view of the varied

TABLE II. Pre-transplant status versus response to transplant

Pre-transplant status	Result following transplant					
	n	Complete response	Partial response	Stable disease	Progressive disease	Died
Chemosensitive						
Complete response 2	10	8	1	0	0	1
Partial response 1	6	6	0	0	0	0
Partial response 2	15	9	4	1	0	1
Chemoresistant						
Stable	3	0	1	0	1	1
Relapse/progressive disease	10	2	1	3	2	2
Total	44	25 (56.8%)	7 (15.9%)	4 (9.1%)	3 (6.8%)	5 (11.4%)

chemosensitive (*n*=31) *v*. chemoresistant disease (*n*=13); complete response 23/31 (74.2%) *v*. 2/13(15.4%), p<0.001

histological subtypes (diffuse large cell 9, mantle cell 5, indolent 2, NK cell 1, peripheral T cell not otherwise specified 1, lymphoblastic 1). The overall response rate was 52.6%; CR in 42.1% (8/19) and PR in 10.5% (2/19). Seven of 8 patients with chemosensitive disease had CR.

Factors affecting response to transplant

The response rate (CR and PR) was higher for patients with good WHO performance status (0 to 2 *v*. 3; 31/37 *v*. 1/7, p<0.0001) and chemosensitive disease (p<0.001). Diagnosis (HL *v*. NHL, 22/25 *v*. 10/19, p<0.07), age (≤35 *v*. >35 years, p=0.18) and sex (males *v*. females; p=0.97) did not affect response to transplant.

Toxicity to conditioning chemotherapy

Gastrointestinal toxicity. Grade III–IV mucositis (20.4%), grade II–III nausea/vomiting (36.3%) and grade II–III diarrhoea (41%) were common non-haematological toxicities. Nine patients required parenteral analgesics to control pain due to mucositis (Table III).

*Renal toxicity***.** Renal dysfunction was seen in 17 of 44 patients; grade I in 11, grade II in 5 and grade III in 1 patient. Clinically the causes were medication-related in 9, tumour lysis in 2 and sepsis with or without medication in 4. In 2 patients the cause could not ascertained. One patient died of acute renal failure.

Liver dysfunction and sinusoidal obstruction syndrome (SOS). Fifteen patients had liver dysfunction, grade I in 10 (22.7%), grade II in 2 (4.5%) and grade III in 3 patients (6.8%). Liver dysfunction was attributed to medication in 4, sepsis in 5, SOS in 2, hepatitis B in 1, recurrent disease in 1 and no cause was found in 2 patients. One patient died of SOS.

Cardiac toxicity. One patient died of severe cardiac toxicity possibly secondary to high dose cyclophosphamide-induced acute myocarditis.

Lung toxicity. Acute grade III pulmonary dysfunction was seen in 2 patients due to pulmonary alveolar haemorrhage (PAH). Both patients recovered.

Haemorrhagic cystitis. One patient had self-limiting cyclophosphamide-induced cystitis.

Central nervous system toxicity. Three (6.8%) patients had somnolence, delirium and tremors (grade I) that resolved without any specific treatment.

Engraftment syndrome. Three patients had evidence of engraftment syndrome. They had weight gain (3/3), fever (2/3), dyspnoea (2/3) and skin rash (2/3). The median time for onset of engraftment syndrome was 11 days (range 10–12 days). All these patients improved gradually after stopping growth factors and with diuretics.

Infections

A total of 56 neutropenic febrile episodes (mean 1.3) were recorded. Infection was documented in 34 patients. This included clinical, radiological or microbiological evidence in 27 patients and central line infection in 7 patients (15.9%). In the remaining 10 patients (22.7%) no focus could be identified (Table IV).

Clinically, pulmonary infections were common (25%) followed by upper respiratory tract and sinusitis (15.9%). Gram-negative bacteria were isolated in 29.5%, Gram-positive in 15.9% and polymicrobial in 2.3% of patients. In 12 patients organisms were

TABLE III. Regimen-related toxicity

Toxicity	Grade 0 (%)	Grade I–II (%)	Grade III–IV (%)
Mucositis	13.6	65.9	20.4
Nausea/vomiting	6.8	88.4	4.5
Diarrhoea	25.0	65.9	9.1
Hepatic	65.9	27.2	6.8
Renal	55.8	36.4	2.3
Pulmonary	95.5	—	4.5
Cardiac	97.7	—	2.3
Central nervous system	84.1	6.8	—
Haemorrhagic cystitis	97.7	2.3	—
Engraftment syndrome	93.2	6.8	—

TABLE IV. Pattern of infections

Infection	*n* (%)
Sites (*n*=44)	
Chest	11 (25)
Upper respiratory tract	6 (13.6)
Sinusitis	1 (2.3)
Gastrointestinal (perianal)	2 (4.5)
Skin	1 (2.3)
Urinary tract infection	1 (2.3)
Central line	7 (15.9)
Hepatitis B	1 (2.3)
Positive chest X-ray	8 (18.2)
Microbiological (blood) isolates	21 (47.7)
Gram-negative	13
Gram-positive	07
Polymicrobial	1
Fungus on biopsy (*Aspergillus*)	2/20 (20 patients received empirical amphotericin B)
Central line isolates	12 (27.3)
Gram-negative	5
Gram-positive	6
Fungus (*Aspergillus*)	1

isolated from the central line and these were Gram-positive in 6 (13.6%), Gram-negative in 5 (11.4%) and in 1 patient a fungus. Twenty-one patients received empirical amphotericin B because of persistent fever. Fungal infection could be confirmed in 3 patients either on biopsy (2) or on culture (1); in all it was due to *Aspergillus*.

Post-transplant, 7 patients (HL 5, NHL 2) developed localized herpes zoster within 6 months. All responded to acyclovir. One patient with HL developed tuberculosis of the spine and responded to antitubercular treatment.

Early mortality (day 30 and day 100)

Five patients died before day 30. The causes of death were sepsis with or without multiorgan failure (2) and regimen-related toxicity (3; acute cardiac toxicity, acute renal failure and SOS in 1 each). Four of these 5 patients had chemorefractory disease and 1 patient was in second PR at the time of transplant. The risk of mortality by day 30 was more in patients with WHO performance status (PS) of 3 compared to those with PS 0 to 2 (3/7 *v.* 2/37 [PS 0–2], p<0.009), chemorefractory disease (p<0.006) and those who failed to engraft by day 18 (p<0.0001). Early (day 30) transplant-related mortality was 11.4%; being higher among patients with pre-transplant chemoresistant disease 23.1% (3/13) *v.* 6.4% (2/31; p=0.11).

Current status and survival

Thirty-nine patients (88.6%) were alive day 100 onwards. Of these 23 are currently alive, 18 disease-free and 5 with disease on salvage chemotherapy; 16 patients have died; relapse being the cause in 15.

At a median follow up of 79 months, the median OS and EFS for patients with HL had not been reached. The mean (SE) OS and EFS was 103.9 (17) (95% CI 70.57–137.15) and 91.2 (15.9) (95% CI 60.06–122.23), respectively. The median (SE) OS in patients with NHL was 12 (6.53) months (95% CI 0–24.80) and EFS was 5 (1.29) months (95% CI 2.47–7.53). For HL and NHL, the estimated mean (SE) OS at 5 years was 78.2 (8.71) and 26.3 (10.1), respectively (Fig. 1). The corresponding figures for EFS were 51.05 (12.7) and 26.3 (10.1), respectively (Fig. 2). Patients who achieved CR and PR following transplant had a better survival (p<0.00001; Fig. 3).

DISCUSSION

We analysed the data on patients with lymphoma to get an insight into transplant-related complications, infections and overall outcome. The median age of HL patients was 29 years and of NHL patient was 48 years. These figures are similar to international data.[5,14] With improved supportive care, more and more eligible patients in the higher age groups are being treated with HDCT and ASCT. Currently, lymphoma (both HL and NHL) is the second most common indication for ASCT worldwide.[14]

Engraftment characteristics were similar to earlier reports (data not shown).[2,3] The median time for hospitalization after stem cell infusion was 19 days which is similar to the international data. Grade II–III nausea/vomiting, grade II diarrhoea and grade III–IV oral mucositis (20% required parenteral analgesics) were the major gastrointestinal side-effects). The use of keratinocyte growth factor (pelifermin) has been associated with reduced risk of mucositis but we did not use it.[15] Major renal and liver dysfunction (grade II–III) was seen in 13.7% and 11.3% of recipients. The frequency and severity of renal dysfunction,[16] liver dysfunction,[17,18] SOS,[19] pulmonary toxicity,[20,21] haemorrhagic cystitis,[22] cardiac[23]

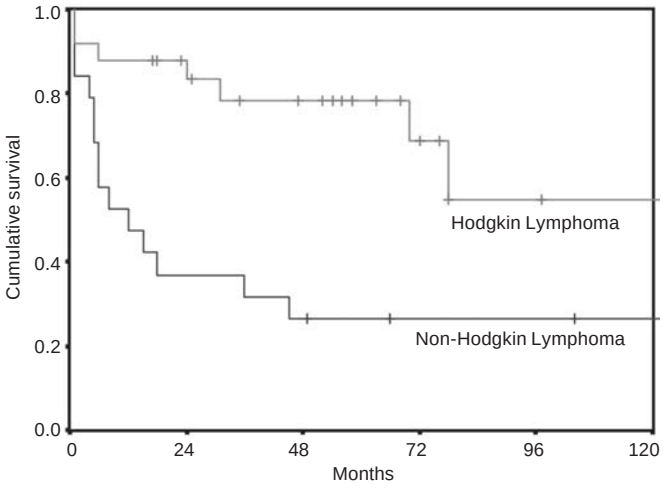


FIG 1. Overall survival according to diease

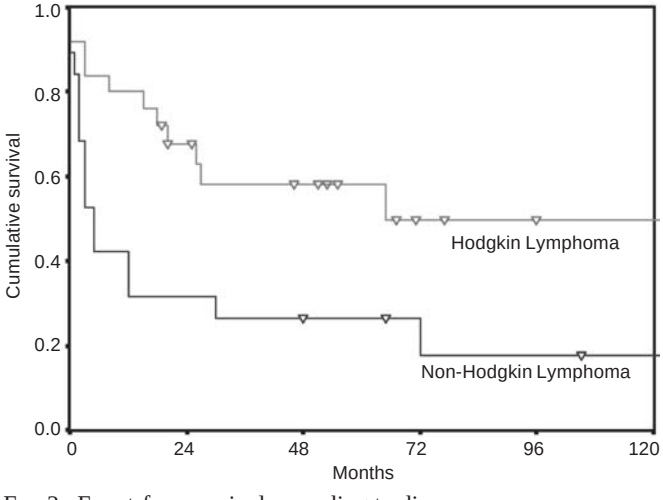
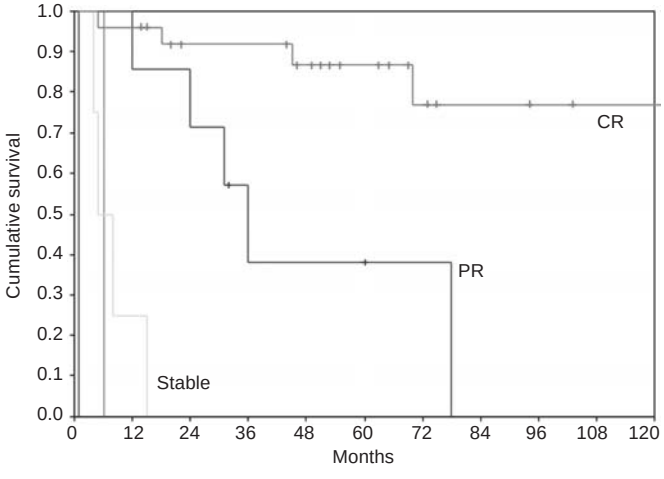


FIG 2. Event-free survival according to diease



Response	Median (SE) overall survival (months)
Complete (CR) (n=25)	172 (0)
Partial (PR) (n=7)	36 (5.23) (95% CI 25.74–46.26)
Stable (n=4)	5 (2.0) (95% CI 1.08–8.92)
Progressive disease	6

FIG 3. Overall survival in relation to response

and central nervous system toxicity[24] was similar to that in previous studies. In our study, 3 of 44 patients (7%) died of regimen-related toxicity.

The risk of transplant-related morbidity and mortality is directly proportional to the recipient's disease and performance status at the time of transplant.[1,11] We found similar results—patients with pre-transplant chemosensitive disease did better than those with chemoresistant disease and those with WHO performance status of 0 to 2 did better than those with performance status 3. These observations are similar to those reported in single-centre studies and in the Center for International Blood and Marrow Transplant Research (CIBMTR) data.[5,14]

Higher response rates and reduced morbidity and mortality among patients with pre-transplant chemosensitive disease argue in favour of adequate pre-transplant therapy and taking patients for ASCT early, i.e. in the first relapse rather than after multiple relapses when the disease is refractory.

Infections (secondary to severe myelosuppression) are the major cause of morbidity and mortality in the early (day 0–30) transplant period. Infections due to Gram-negative organisms were higher in our study, compared to earlier reports.[25,26] A higher frequency of Gram-negative organisms was also observed in a recent study of patients with acute myeloid leukaemia at our centre.[27] Gram-positive organisms were predominant isolates from the central line, similar to earlier reports.[28] Sepsis with multiorgan failure was the cause of death in 4.5% in our study. This too is similar to that in earlier studies[3,4,9] and the CIBMTR data (8%).[5,14] About half our patients (19 of 44) received empirical amphotericin B; this is similar to the experience at other centres.[29] However, fungal organisms could be cultured in only 3 patients. It is important to reiterate that all these transplants were done in single rooms without any HEPA filter or laminar airflow facilities.[30,31] Due to a higher probability of fungal infections in our set up,[27] we have a policy of starting amphotericin B by day 4–5 if the fever does not resolve or if there are radiological signs suggestive of a fungal infection.

Following ASCT, relapse remains the major cause of failure. Among 39 of our patients (88.6%), who were alive at day 100, 21 relapsed, 15 died and the remaining 6 patients are currently on salvage therapy. In the CIBMTR study, relapse was the main cause of death (73%).[14] Haioun *et al*. have recently reported the use of rituximab (anti-CD20 antibody) for post-ASCT maintenance in patients with diffuse large B cell NHL. At a median follow up of 4 years there was a non-significant trend for increased EFS in the rituximab arm (80% *v*. 71%, $p<0.09$). However, rituximab was not used during induction therapy.[32]

The median OS was significantly higher among patients transplanted in PR1 compared with those transplanted in CR2 and PR2 which, in turn, was higher than those transplanted with relapsed or refractory disease. These observations are in accordance with earlier studies[3–5,14] and confirm the superior outcome of patients with chemosensitive disease. A small number of patients and varied histological subtypes (heterogeneity) in NHL are the main limitations of our study. Yet, 5-year EFS of 51% and 26% for HL and NHL, respectively, confirms earlier observations that ASCT results in improved long term outcome in a proportion of patients, especially in those with chemosensitive disease before ASCT. Good primary management and careful case selection (chemo-sensitive disease) and decision to transplant after first chemosensitive relapse are major factors associated with improved outcome.

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