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# Relapse of lymphoma after allogeneic hematopoietic cell transplantation: Management strategies and outcome

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## Abstract

**Objective—**The outcome and management of relapsed lymphoma after allogeneic hematopoietic cell transplantation (HCT) is difficult. Therapeutic options may include donor lymphocyte infusion (DLI), reduction of immunosuppression (RIS), chemotherapy, radiation, immunotherapy, second HCT and experimental treatments, but reported data contrasting the response and efficacy of these salvage treatments is limited. We describe the treatments, response, prognosis and long-term survival of 72 patients with relapse of lymphoma after allogeneic HCT.

**Results—**Between 1991 and 2007, 227 lymphoma patients underwent allogeneic HCT. Of these, 72 (32%) developed relapse/progression after their HCT at a median of 99 days (0–1898 days); 37 had early (<100 days) post-HCT relapse. Forty-four had non-Hodgkin's lymphoma (7 mantle cell, 5 indolent, 15 diffuse large B cell, 4 Burkitt's and 13 T/Natural Killer cell) and 28 patients had Hodgkin's lymphoma. At the time of HCT, 62 patients were in remission (22 in complete [CR] and 40 in partial [PR]), one had stable while 9 had progressive disease. Seventeen cases received myeloablative and 55 received a reduced intensity conditioning regimen. At relapse, most patients had generalized lymphadenopathy, extranodal organ involvement and advanced disease. Five patients received no intervention for the post-HCT relapse. Immunosuppressive treatment was reduced or withdrawn as the first line therapy in 58 patients (80.5%); 47 were treated using combinations of conventional chemotherapy (n=22), rituximab (n=27), interferon (IFN) (n=1), DLI (n=7), second HCT (n=2), local radiation (n=23) and other therapy (n=6). Thirty-eight patients had an objective response (CR in 30, PR in 8) and 2 had stable disease (SD). At the post-HCT relapse, favorable prognostic factors for survival after HCT included good ECOG performance status (0–2), normal lactate dehydrogenase (LDH), early stage disease (stage I–III), isolated extranodal organ involvement and later relapse (>100 days) post-HCT. Three year survival after HCT was significantly better in late than early relapse (53% (95% confidence interval (CI) [34–69%] vs. 36%, [20–52%], p=0.02). Of 72 relapsed patients, 29 (40%) survive at a median of 34 (3–148) months post transplant. The most common cause of death was underlying lymphoma (79%).



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**Conclusion—**The overall prognosis of relapsed/progressive lymphoma after allogeneic HCT is disappointing, yet half of patients respond to withdrawal of immunosuppression and additional therapies. Novel treatments can control lymphoma with acceptable morbidity. Particularly for patients with later relapse, ongoing treatment after relapse can yield meaningful benefit and prolonged survival.

### Keywords

Allogeneic hematopoietic cell transplantation; lymphoma; relapse

## Introduction

Hematopoietic cell transplantation (HCT) has been widely used as a treatment modality in relapsed and aggressive lymphoma, most often using an autologous graft (1–3). For the past decade, allogeneic HCT, particularly using reduced intensity conditioning (RIC) has become another potential curative treatment option, even in patients with relapse or progression following autologous HCT (4–7). However, the management and outcome of relapse after allogeneic HCT is uncertain and poorly described (8). Most available data are limited to donor lymphocyte infusions (DLI) which sometimes provide durable clinical response (9–11). Other modalities include withdrawal of immunosuppression, rituximab, chemotherapy, radiation, a second allograft or a combination of therapies. There are only limited data detailing the response and efficacy of these salvage treatments in relapsed lymphoma. Bethge et al reported on patients with relapse or progression after non-myeloablative allogeneic HCT (12) and in a small cohort, 48% survived at 24 months following the post-HCT relapse. We report on the outcome and response to salvage treatment of 72 patients with relapsed lymphoma following allogeneic HCT.

## Patients and Methods

A total of 227 lymphoma patients underwent allogeneic HCT at the University of Minnesota between January 1991 and December 2007. We identified 72 patients who developed relapsed or progressive disease after HCT. Patients' data were retrieved from the University of Minnesota Blood and Marrow Transplantation Program Database which contains specified and prospectively collected data for all patients transplanted at our center. This was supplemented by detailed review of all treatment and response data from available medical records. Data and outcomes were analyzed as of December 2009. Pre-transplant characteristics included age, gender, chemosensitivity, lymphoma histopathology and disease status at HCT. Lymphoma histologies were grouped for analysis as: Indolent lymphoma (Chronic lymphocytic leukemia/small lymphocytic lymphoma, marginal zone lymphoma and follicular lymphoma); Aggressive lymphoma (Mantle cell lymphoma, diffuse large B cell lymphoma (DLBCL), T cell/Natural Killer (T/NK) cell lymphoma; Highly aggressive lymphomas were Burkitt NHL. Patients underwent allogeneic HCT using myeloablative or RIC regimens. Graft sources included bone marrow, filgrastim-mobilized peripheral blood (PBSC) from related or unrelated donors (URD) or unrelated umbilical cord blood (UCB).

In addition to demographics and pre-HCT disease characteristics, a variety of post HCT parameters were considered in univariate analyses to predict outcomes including: best response achieved from HCT, time to progression/relapse, relapse sites (nodal and extranodal organ), number of nodal area involvement (locoregional or 1–3 nodal area [stage I–II] vs. diffuse or > 3 nodal area [stage III]), bulky disease (any tumor mass >10 cm in diameter; or a mediastinal mass > 1/3 chest diameter), lactate dehydrogenase (LDH) and Eastern Cooperative Oncology Group (ECOG) performance status at the time of relapse.

Salvage for relapse/progressive disease after HCT and therapeutic responses were reviewed. Treatment response was determined by using clinical assessment, biochemical and radiographic investigation as complete remission (CR), partial remission (PR), stable disease (SD) or progressive disease (PD) according to 2007 revised response criteria for malignant lymphoma (13). We determined the overall survival (OS) after allogeneic HCT and survival from the time of relapse to last follow up or death. Severe treatment-related complications (≥ grade 3) defined by National Cancer Institute Common Terminology Criteria for adverse events (CTCAE) version 3.0 were recorded.

### Statistical Analysis

Patients and transplant characteristics between groups were compared using chi-square or Fisher's exact test for categorical data and Wilcoxon's rank-sum test for continuous data. OS was analyzed by using the Kaplan-Meier method with 95% confidence intervals (CI) and comparisons between groups used the log rank test. All statistical analyses were performed with Statistical Analysis System statistical software version 9.2 (SAS Institute, Inc., Cary, NC) with p value ≤ 0.05 considered statistically significant. Patients and/or their parents/guardians had exercised written informed consent for protocol specified treatment and prospective data collection on their outcomes. The University of Minnesota Institutional Review Board granted specific approval for this secondary data retrieval and analysis.

## Results

### Pre-transplantation Characteristics

Seventy-two patients had relapsed or progressive lymphoma following allogeneic HCT (Table 1). Median age at the time of HCT was 40 (4–62) years. Forty-four patients had non-Hodgkin lymphoma (NHL) (7 mantle cell, 5 follicular/marginal zone/small lymphocytic/chronic lymphocytic leukemia, 15 DLBCL, 4 Burkitt and 13 T/NK cell) and 28 had Hodgkin lymphoma (HL). The median number of pre-HCT chemotherapeutic regimens was 4 (range 1–11). Twenty-three patients underwent previous autologous HCT before the allogeneic HCT. At the time of allogeneic HCT 62 (86%) had chemosensitive disease (22 were in CR; 40 PR), 1 had stable and 9 (13%) had progressive disease. Seventeen patients received myeloablative and 55 a RIC regimen. UCB grafts were used more frequently (56%) than sibling donor granulocyte filgrastim-mobilized PBSC (33%) and marrow grafts (11%): 4 from siblings and 4 from URD.

### Post-transplantation Relapse or Progression

The median time to post-allogeneic HCT relapse or progression was 99 days (range 0–1898 days); 37 patients (51%) had early progression or relapse (within 100 days). Table 2 shows disease characteristics at the time of relapse or progression. Nodal relapse occurred in 65 patients (90%). Of these, 41 patients (57%) had diffuse nodal involvement and 23 (32%) had bulky disease. Fifty-six patients (78%) had at least one extranodal relapse site (bone marrow 20, lung 27, gastrointestinal 11, musculoskeletal 19 and central nervous system (CNS) 2). At relapse, LDH was elevated in 20 of 52 tested (44%). Seventeen patients had poor performance status (ECOG 3 or 4) at the time of relapse/progression.

### Treatment of Relapsed lymphoma

Salvage treatments of relapse/refractory lymphoma after allogeneic HCT were tailored individually based upon the timing of relapse, performance status, extent of disease, pre-HCT treatment and underlying co-morbidities including active graft versus host disease (GVHD) (Table 3). Five patients received no intervention at the time of relapse/progression due to poor performance status or advanced stage of lymphoma. In 67 patients who received

salvage treatment, reduction of immunosuppression (RIS) was the first line therapy in 58 patients (81%) and was the only initial treatment in 36 patients.

Systemic therapies were used either alone or combined with other treatment (RIS, chemo-immunotherapy or rituximab). Fourteen patients received chemotherapy alone, 20 had rituximab alone and 7 had combined chemo-immunotherapy. Vinca alkaloid (vinblastine/navelbine)-containing regimens were used most often (12 patients). Other treatments include interferon (IFN) (n=1), second HCT (n=2) and novel therapeutic agents (n=6). DLI (not available for the 40 UCB recipients) was given to 7 patients. Local radiation (n=23) accompanied RIS and other systemic therapies. One patient had surgical resection of a mass to relieve compressive symptoms.

## Response to Treatment and Survival

Of 67 patients who received treatment for their relapsed disease, 38 patients had an objective response (30 CR, 8 PR; overall response rate 52%) while 2 had SD and 30 had PD; 2 were not further evaluated. The median time to best response was 7.1 months (range, 1–70 months). Of 38 patients who achieved response, 24 patients responded (15 CR, 9 PR) to the initial salvage regimen [RIS (n=13), combined systemic treatment (n=5), chemotherapy (n=2), radiation (n=3) or DLI (n=1)]. RIS alone induced CR in 10 cases (HL 4, T/NK cell lymphoma 4, mantle cell 2) (Table 4). In those who achieved CR, the median progression free survival (PFS) was 19 months (range, 0.3–132 days). In 9 patients with PR, the median PFS was 1.5 months (range, 0.3–4.3 months), but all PR patients later progressed. Twenty-seven patients responded to second line salvage treatment (21 CR, 6 PR) (Table 4). Of 21 patients who received second line treatment with chemotherapy, 9 responded (5 PR, 4 CR) and 1 had SD.

The median duration of response from chemotherapy was 6 months (range, 2–74 months). Among 9 patients who had objective response to chemotherapy, five had HL, two T/NK, one DLBCL and one Burkitt's NHL. Six of 9 patients received vinca-alkaloid containing regimens. Gemcitabine was used as a single agent or combined with vinblastine or navelbine in 3 patients. Rituximab, either alone or in combination, induced response in 12 of 27 (44%) patients (7 DLBCL, 2 follicular, 2 mantle and 1 HL). Of the 12 patients who responded to rituximab (alone or in combination with other therapies) for their post-HCT relapse, 10 had previously received rituximab and all but 1 had responded (CR/PR). Rituximab responses for the post-HCT relapse were modestly durable lasting 1–68 months (median 23 months). Somewhat surprisingly, 6 of the 7 (85%) patients who received DLI achieved remission (4 HL and 2 T/NK cell NHL).

Objective to any therapy prolonged survival as the 38 patients who responded (CR/PR) to post-HCT therapy had median survival of 30 months (range, 0–150 months) after relapse and 36 months (range 3–148 months) after allogeneic HCT (Figure 2). Patients who did not respond had median survival of only 2 (0–26 months) months after relapse; five months (range 1–32 months) after HCT.

Twenty-nine patients survive at last follow up (17 in CR, 2 PR, 3 SD and 7 PD) (Figure 1). In univariate analysis, performance status [ECOG PS 3–4 vs. 1–2, median survival 1.1 months, (95% CI, 0.2–1.9) vs. 18.3 months, (17.2–81.2, $p<0.001$] and LDH [elevated LDH vs. normal LDH, median survival 2.1 months, (95% CI 1.3–2.9) vs. 9.1 months, (14.8–93), $p<0.001$] had a significant and unfavorable impact on overall survival and also on survival after the post-HCT relapse (not shown). The pathologic subtype of lymphoma had a marginal impact on survival outcome ($p=0.05$) with no survivors in those with Burkitt's NHL (Figure 2B). Age (<40 vs. ≥ 40), chemosensitivity, stem cell source (UCB vs. PBSC/BM), conditioning regimen (myeloablative vs. RIC) and number of treatment regimens prior

to transplantation (<4 vs. ≥) did not impact overall survival or survival after transplant relapse.

Patients with later post-HCT relapse (>100 days) had better survival than those with early relapse, 3-year survival 53% vs. early relapse 36% ($p$=0.02) (Table 4B, Figure 1C). In addition to late relapse, patients who achieved remission (CR/PR), those with stage I–III disease at relapse or those with isolated nodal or extranodal disease at relapse had better 3-year survival after HCT (Figure 2), however, none of these factors factors had prognostic impact on survival after transplant relapse. The most common cause of death was due to underlying lymphoma, which accounted for 79% of all deaths. Other causes of death included infection (n=3), severe GVHD (n=2), diffuse alveolar hemorrhage (n=1) and liver failure (n=1).

### Complications Following Treatment of Relapse

Treatment related adverse events were recorded. Following treatment of relapse, 13 patients developed severe cytopenias requiring transfusion or growth factor support. Severe infection occurred in 12 patients. Acute GVHD after RIS or second allogeneic HCT was moderate-severe GVHD in only 13 patients (Grade II in 9, Grade III–IV in 4). All 7 patients who received DLI developed acute GVHD, but severe acute GVHD (grade III–IV) occurred in only 2 (28%).

## Discussion

Recurrent lymphomas have become an increasingly therapeutic challenge. Allogeneic HCT has been more commonly used as a potential curative option due to recognition of the graft versus lymphoma effect with recent reports describing improved outcomes and limited treatment related adverse events (6, 14, 15). However, progression or relapse after HCT remains common and a major cause of death (15). Importantly, we found that some patients had prolonged survival following their relapse, particularly those with later relapse following the allograft. However, the overall prognosis for our patients with relapsed/progressive lymphoma following allogeneic HCT is poor with a median survival of only 5 months after HCT (2 months following relapse, similar to the few other reports (12, 16).

Prognostic factors that modify outcome after allogeneic HCT include low transplant comorbidity index (HCT-CI) scores, conditioning regimen, age, type of lymphoma, prior cytomegalovirus (CMV) infection and graft source (7). In our study, the major prognostic factors that determined overall survival survival after HCT and survival following relapse include LDH at the time of relapse, ECOG performance status, stage and sites of relapse. The time of relapse after transplantation also affected post transplant survival, but not survival after the relapse. We observed no prognostic impact of graft source, conditioning regimen intensity or lymphoma histological subtype on survival after transplant relapse. Due to small number of patients, multivariate analysis was not performed. Most earlier reports of allogeneic HCT in lymphoma (4–7, 14, 15, 18) did not examine post relapse management, response or subsequent survival.

Several brief reports described salvage treatment in relapsed/progressive lymphoma following HCT; mostly relapse after autologous HCT (19–28). A few series describe allogeneic HCT for those who respond to other salvage treatments. Reports of salvage therapies after allogeneic HCT are limited and there are no standard guidelines for the treatment of post-allograft relapse. Available potential treatment approaches include RIS, chemotherapy, rituximab, DLI (9, 10, 29), second allogeneic HCT (30, 31), interleukin-2 (32) or other novel agents (33, 34) yet reported outcomes are disappointing. One small series described salvage treatment for NHL after autologous (n=46) and allogeneic (n=12) HCT

(16). The median survival after allografting was only 7 months and no specific therapy was recommended.

Reduction of immunosuppressive is often a first step in patients without severe GVHD or highly aggressive NHL (11, 35). In our study, some patients with HL, T/NK cell or mantle cell NHL achieved CR with RIS alone while indolent B cell lymphoma and highly aggressive lymphoma such as Burkitt's lymphoma rarely responded to RIS, even with other therapies. A durable response to RIS observed in some patients might reflect a potent graft versus lymphoma effect, but we observed no correlation with specific histologies.

Rituximab, in addition to its application as an approved first line treatment for CD20+ NHL, has been increasingly used for relapsed/progressive lymphoma with promising efficacy and infrequent treatment-related adverse events (36). Following HCT, several studies reported its efficacy as a single agent or in combination, mostly following autologous HCT (25, 37–39). We observed that rituximab could induce responses in some patients, even if previously treated with rituximab. Most of these patients had NHL (DLBCL 7, indolent 2, mantle cell 2) and one had HL. However, no study prospectively tested rituximab as a salvage treatment for prevention or therapy of relapse after allogeneic HCT.

Several chemotherapeutic regimens were used, but we could not compare the efficacy of different regimens due to small numbers and treatment heterogeneity. Moreover, the selection of chemotherapeutic regimen was influenced by many variables including previous response, performance status, histopathology and lymphoma burden. Notably, most of patients in our series who responded to chemotherapy had HL whereas those with NHL rarely responded unless treated concomitantly with rituximab. It is interesting to note that chemotherapy plus rituximab provided a therapeutic effect in this highly refractory patient subgroup who had exhausted several earlier treatment modalities. This might reflect a combined graft versus lymphoma effect from the concomitant reduction in immunosuppression. This was also was demonstrated by the promising responses to DLI in our study. However, this hypothesis will need further research to demonstrate its therapeutic potential.

DLI are used as a rescue treatment in relapsed lymphoma following allogeneic HCT with mixed results. Most early reports of DLI described favorable responses, but mostly in chronic myeloid leukemia (40). Some recent reports include indolent NHL (10, 29). We observed promising responses after DLI in of 7 patients including HL and T cell NHL. In our series, the large number of UCB graft recipients could not receive DLI.

Second allogeneic HCT for lymphoma is rarely reported and has high treatment related mortality (30, 31). This may be due to patients' poor performance status, extensive previous treatment and refractory disease. Baron et al reported the feasibility of RIC allogeneic HCT in patients who had failed a first myeloablative HCT (autologous or allogeneic) (31) with median overall survival of 813 days. However, the patients were heterogeneous and only 10 (of 147) had undergone a previous allogeneic HCT, none for NHL or HL. Another series describe only modest morbidity/mortality of second myeloablative allogeneic HCT in pediatric patients, especially age < 10 years (30). Recently, Kenkre and colleagues demonstrated promising long-term survival from T-cell depleted allogeneic HSCT in multiply relapsed lymphoma (17). However, there were only four patients who had a prior allotransplant preceding the allogeneic transplant reported. We might consider that a second allogeneic transplantation might be a feasible option if DLI is unavailable.

The prognosis and response to salvage treatment in relapse/progressive lymphoma following allogeneic HCT are rarely reported. Acknowledging the limits of retrospective analysis and heterogeneity of patients, histologies and treatments, we are encouraged that for some

patients, especially those with later relapse, combination approaches can again achieve durable CR and prolonged survival. Improvements in supportive care and development of novel therapies may further improve outcome for such patients, but careful clinical study is needed to dissect the best approaches and identify those most likely to benefit.

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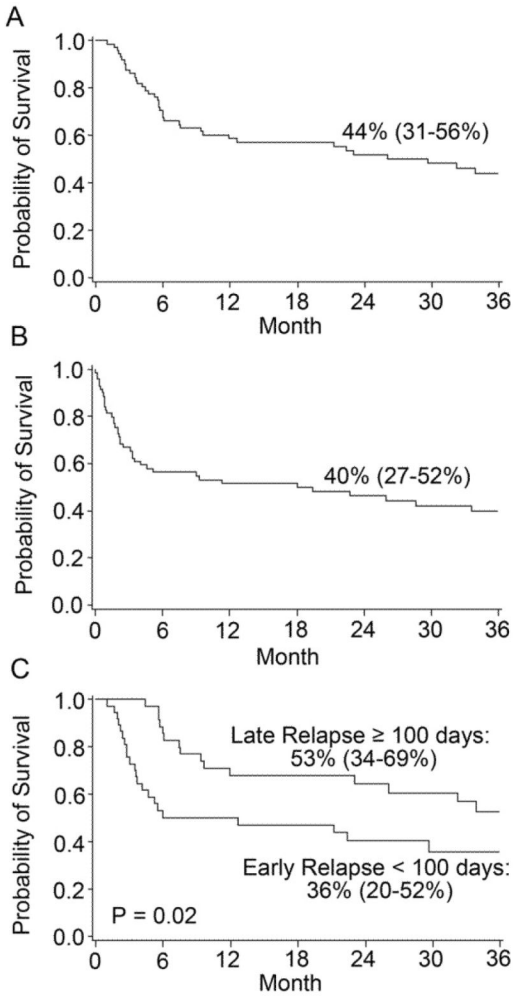


**Figure 1.**

A) Overall survival after allogeneic HCT; B) 3 year Survival following relapse after allogeneic HCT; C) Overall survival following allogeneic HCT in early (<100 days) vs. late relapse.

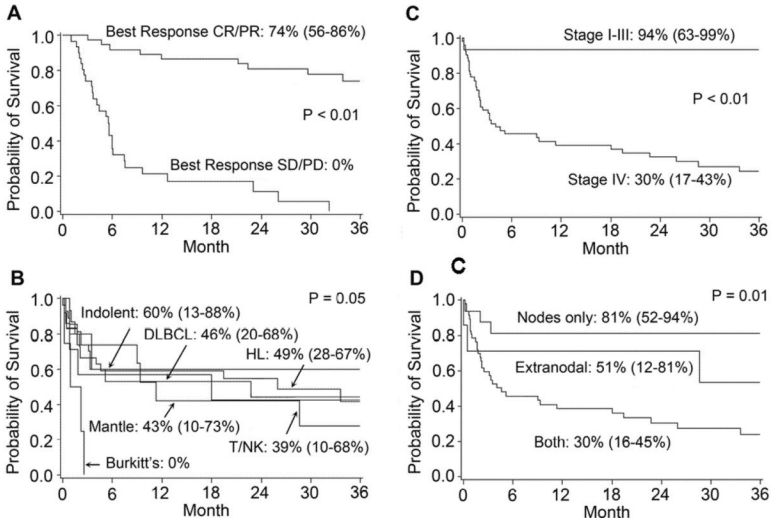


**Figure 2.**

Survival after allogeneic HCT.

A. Responders CR/PR vs. SD/PD.

B. Histologic subsets

C. Stage at relapse (Stage I–III vs. IV)

D. Site of relapse (nodes vs. extranodal vs. combined sites)

**Table 1**

Characteristics of relapsed patients after allogeneic HCT

| | N=72 |
|---|---|
| Median age, years (range) | 40 (4–62) |
| Gender, M/F | 42/30 |
| Histopathology | |
| Non Hodgkin lymphoma | 44 (61%) |
| B Cell Lymphoma | 31 (43%) |
| Indolent lymphoma[α] | 5 (7%) |
| Aggressive lymphoma[ß] | 22 (30%) |
| Burkitt's lymphoma | 4 (6%) |
| T/NK cell lymphoma | 13 (18%) |
| Hodgkin lymphoma | 28 (39%) |
| Median number of regimens before HCT[§] | 4 (1–11) |
| Chemosensitive disease at HCT | 62 (86%) |
| Previous autologous HCT | 23 (32%) |
| Conditioning regimen for allogeneic HCT | |
| Myeloablative | 17 (24%) |
| Reduced Intensity | 55 (76%) |

[α]Indolent lymphoma: Chronic lymphocytic leukemia/Small lymphocytic lymphoma, marginal zone lymphoma and follicular lymphoma.

[ß]Aggressive lymphoma: Mantle cell lymphoma (n=7), diffuse large B cell lymphoma (n=15).

[§]HCT: Hematopoietic cell transplantation.

**Table 2**

Presentation of relapsed and progressive lymphoma after allotransplantation

| | N=72 |
|---|---|
| Median time to relapse or progression (days) | 99 |
| (range) (inter-quartile range) | (0–1898) (43–194) |
| | N (%) |
| < 100 days | 37 (51%) |
| 100–179 days | 13 (18%) |
| 180–365 days | 15 (20%) |
| >1 year | 7 (10%) |
| Sites of relapse | |
| Isolated extranodal relapse | 7 (10%) |
| Isolated nodal relapse (Stage I–III) | 16 (22%) |
| Combined nodal and extranodal (Stage IV) | 49 (68%) |
| Sites of extranodal relapse | |
| Bone marrow | 8 (11%) |
| Visceral | 20 (28%) |
| Musculoskeletal | 6 (8%) |
| Multiorgan involvement | 22 (31%) |
| Performance status (ECOG) at relapse | |
| 0–2 | 55 (76%) |
| 3–4 | 17 (24%) |
| Elevated LDH at relapse | 23/52 (38%) |

ECOG: Eastern Cooperative Oncology Group, LDH: Lactate dehydrogenase

**Table 3**

Treatment for relapse after allotransplantation

| | N (%) |
|---|---|
| No treatment | |
| Reduction of Immunosuppression (RIS) | 5 (7%) |
| Systemic treatment | 58 (81%) |
| Chemotherapy | 14 (19%) |
| Rituximab | 20 (28%) |
| Chemotherapy + rituximab | 7 (10%) |
| Interferon | 1(1%) |
| Donor Lymphocyte Infusion (DLI) | 7 (10%) |
| Involved field radiation | 23 (32%) |
| Surgical Resection | 1 (1%) |
| Second allogeneic HCT | 2 (3%) |

Patients could receive more than one treatment, thus the total is greater than 100%.

## Table 4

Response and survival following relapse after allogeneic HCT

**A. All patients**

| | N=72 |
|---|---|
| Response to first treatment | |
| CR/PR | 24 (33%) |
| SD/PD | 42 (58%) |
| Unknown response | 6 (8%) |
| Best Response achieved | |
| CR/PR | 30/8 (42/10%) |
| SD | 2 (3%) |
| PD | 29 (40%) |
| Time to best response after relapse (median range) months | 7.1 (1–70) |
| Treatment preceding best response | |
| Reduction of Immunosuppression (RIS) | 30 (42%) |
| Chemotherapy | 11 (15%) |
| Rituximab | 9 (13%) |
| Chemo-immunotherapy | 9 (13%) |
| Radiation | 3 (4%) |
| Second allogeneic HCT | 1 (1%) |
| DLI | 5 (7%) |
| Survival, median (95% CI) months | |
| After HCT | 34 (3–148) |
| Afterpost-HCT relapse | 25 (0–145) |

**B. Early vs. late relapse.**

| | Early Relapse (<100 days post HCT) (n=37) | Late Relapse (≥100 days post HCT) (n=35) | p-value |
|---|---|---|---|
| 3 year survival following HCT (95% CI) | 36% (20–52%) | 53% (34–69%) | 0.02 |
| 3 year survival following relapse | 36% | 44% | 0.26 |
| Best response to treatment* | | | 0.67 |
| CR/PR | 18 (49%) | 20 (57%) | |
| SD/PD | 18 (49%) | 13 (37%) | |

CR, Complete, Remission; PR Partial remission; SD Stable disease; PD Progressive disease

*Three patients were not evaluated.