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Outcome in Patients with Diffuse Large B Cell Lymphoma who Relapse after Autologous Stem Cell Transplantation and Receive Active Therapy. A Retrospective Analysis of the Lymphoma Working Party (LWP) of the European Society for Blood and Marrow Transplantation (EBMT).

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ABSTRACT

Background. Autologous hematopoietic stem cell transplantation (auto-HSCT) is the standard of care for patients with diffuse large B cell lymphoma (DLBCL) who relapse/progress after first line chemo-immunotherapy strategies. Long-term outcome of those who relapse after transplant is largely unknown.

Patients and Methods. We retrospectively analyzed a group of 256 adult patients with DLBCL reported to the EBMT registry who relapsed after an auto-HSCT performed between January 2003 and December 2013 and who received active salvage strategies at relapse.

Results. One hundred and fifty-four patients (60%) were male; the median age was 53 years at the time of relapse. The median time to relapse was 7 months, with 65% relapsing during the first year after transplantation. Overall response rate after salvage therapy was 46%. With a median follow up of 40 months after first salvage [Interquartile Range (IQR) 23-63 months], overall survival (OS) at 3 years after first salvage was 27% (95%CI 22-33) for the whole group. Eighty-two patients (32%) had a second HSCT, including an allogeneic hematopoietic stem cell transplantation (allo-HSCT) at a median time of 6.5 months after relapse in 69 cases. OS at 3 years after allo-HSCT was 36% (95%CI 25-51). Three-year OS after first salvage of patients relapsing longer than one year after auto-HSCT was 41% (95% CI 31-53) compared to 20% (95% CI 14-24) in those who relapsed in less than 1 year.

Conclusions. The prognosis of patients with DLBCL that relapse after auto-HSCT is dismal. Management of patients who relapse in less than one year after auto-HSCT remains an unmet need. These patients should be considered for CAR-T cell therapy or clinical trials, whilst patients who relapse after one year can be potentially rescued with salvage therapies and a second HSCT. These results provide a benchmark to compare data of new prospective studies that might be conducted in this patient population.

Key Words. Diffuse large B cell lymphoma, autologous stem cell transplantation, prognostic factors, relapse after autologous transplant, duration of first complete remission.

KEY MESSAGES

- Patients with diffuse large B cell lymphoma that relapse after autologous stem cell transplantation have a poor outcome.
- The duration of the complete remission after autologous transplant predicts long-term outcome.
- A significant proportion of the patients are young and with a good performance status; new treatment strategies should be sought for them.

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma, comprising around 30% of all new cases [1,2]. The standard first-line treatment is combination immunotherapy with rituximab and an anthracycline-based chemotherapy such as cyclophosphamide, adriamycin, vincristine and prednisone (CHOP) [3,4]. While many patients who receive this treatment achieve long-term disease free intervals and can be considered cured, 30-40% of them experience relapse or do not respond to first line therapy. The standard of care for relapsed or refractory DLBCL patients who are eligible for intensive therapy, is salvage immuno-chemotherapy followed by consolidation with high dose therapy and autologous hematopoietic stem cell transplant (auto-HSCT) in responding patients [5]. A number of variables present at the time of first relapse of DLBCL or immediately before auto-HSCT have been evaluated with regards to their influence on the risk of relapse following transplantation [6].

Although sustained remissions after auto-HSCT have been reported, 50%-70% of the patients will ultimately develop recurrence of the disease. Historically, patients with disease progression following auto-HSCT have an extremely poor prognosis with a median overall survival (OS) of 3-9 months, and there is no consensus on the optimal therapy for these patients [7,8]. Therapeutic options are heterogeneous, and include salvage chemotherapy followed or not by a second HSCT (autologous or allogeneic) [9-12], clinical trials with new drugs, radiotherapy, palliative care and in recent months chimeric antigen receptor (CAR) modified autologous T cells [13,14]. However, there is currently little information on the outcome for patients whose disease recurs after auto-HSCT and their clinical course.

The aim of the present study is to describe the clinical management and outcome of patients with DLBCL relapsing after auto-HSCT using the European Society for Blood and Marrow Transplantation (EBMT) database.

PATIENTS AND METHODS

Study Design and Inclusion Criteria

This is a retrospective registry-based multicenter study. Data were provided and approved for this study by the Lymphoma Working Party (LWP) of the EBMT. The EBMT is a voluntary working group of more than 600 transplant centers that are required to report all consecutive HSCT and follow-up once a year. Audits are routinely performed to determine the accuracy of the data. Since January 1, 2003, all transplant centres have been required to obtain written informed consent prior to data registration with the EBMT, following the Helsinki Declaration of 1975.

Patients with DLBCL ≥ 18 years old, who relapsed after an auto-HSCT performed between January 2003 (since immuno-chemotherapy became standard therapy in DLBCL) and December 2013 , and reported to the EBMT registry as having relapsed or refractory disease after a first auto-HSCT, were identified. Data for this study were obtained from the lymphoma registry files (minimal essential data Med-A form) and extended by a specific questionnaire (Med-C form) sent to all participant transplantation centers to obtain data regarding characteristics of the patients and outcome after auto-HSCT failure.

A total of 541 patients were identified, but information on therapy after auto-HSCT relapse was not reported in 164. This group of patients was more heavily pretreated before auto-HSCT [3 or more lines in 65 (40%) vs 85 (22%); $p<0.0001$], and had a shorter time from auto-HSCT to relapse [median: 3.5 months (mo) vs 5.7 mo; $p=0.002$] than the 377 patients with available data on post auto-HSCT therapy.

The PIs of the study review all available data on treatment for relapse after auto-HSCT and arbitrarily classified them as having ‘palliative’ or ‘active’ therapy. ‘Palliative’ treatment was considered in patients who received only steroids, radiotherapy or single agent chemotherapy. Among the patients with known therapy, 121 patients received palliative therapy after relapse. These patients were older [median age at relapse: 58 years; p=0.009] and had a shorter time from auto-HSCT to relapse [median: 4.1 mo; p<0.0001]. Patients were considered to have received ‘active therapy’ if they had received chemotherapy regimens including drugs used in routine first or second line protocols for DLBCL (i.e anthracycline or platin compounds) or agents known to result in a prolonged response duration. ‘Active’ regimens were categorized as ‘platinum containing regimens’, ‘active intensive combinations’ (including anthracyclines, cytarabine, ifosfamide or gemcitabine) or ‘active non-intensive combinations’ (including lenalidomide or bendamustine). This study focuses in the group of 256 patients who received ‘active therapy’ after first auto-HSCT relapse (Figure 1).

Definitions

Diagnosis was based on local clinical and histological review. Patients were staged according to the Ann Arbor system. Disease status at transplantation was classified as complete remission (CR), partial remission (PR), or active disease [stable disease / progressive disease (SD/PD)]. Disease status was assessed by each investigator according to standard response criteria at the time of evaluation and to the institutional standard of care.

Statistical analysis

The database was closed for analysis as of June 2017. Descriptive statistics was used to summarize patient’s characteristics. The primary endpoint of the analysis was OS after relapse. OS was calculated from the time of salvage therapy after auto-HSCT to death

from any cause. Kaplan-Meier's method and the log-rank test were used to identify differences in survival between subgroups.

Univariate analysis for survival was performed with a Cox regression model. The variables examined at the time of relapse were: age (older than 50 yr vs younger), gender, B symptoms, bulky disease (> 5 cm vs ≤ 5 cm), Karnofsky performance status score (< 80% vs ≥80%), LDH (elevated vs normal), and time from 1st auto-HSCT to relapse (< 1 year vs ≥ 1 year). All analyses were performed at a 95% confidence interval and differences were considered statistically significant when the *p* value was less than *0.05.* All analyses were performed using R version 3.1.1 with the R packages survival version 2.38, cmprsk version 2.2-7 and Hmisc version 3.16-0 (R Core Team. R: a language for statistical computing. 2014. R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patients' characteristics

Clinical characteristics of the patients at diagnosis and the time of relapse after auto-HSCT are summarized in Table 1.

Treatment after auto-HSCT failure

Salvage therapies used at relapse after first auto-HSCT are shown in Table 2.

Response rate after salvage therapy was: CR in 63 (29%) patients, PR in 36 (17%), SD/PD in 111 (52%), and death without response assessment in 5 (2%). In 41 patients response was not reported.

Eighty-two (32%) patients underwent a second HSCT [allogeneic HSCT (allo-HSCT) in 69 patients]; 32 of them were in CR, 14 in PR, 33 with active disease, and in 3 patients, status was unknown.

Overall survival after first salvage treatment post auto-HSCT

The median follow-up of alive patients was 40.1 months (IQR 22.6-62.6); 191 patients (75%) died: 151 (79%) due to disease progression, 29 (15%) due to transplant related mortality, 2 (1%) of secondary malignancies, and 9 (5%) from other causes. The median OS was 9.7 months (95%CI: 8.3-12.0). OS at 3 years for the whole cohort was 27% (95% CI 21.9-33.3) (Figure 2). For patients who received an allo-HSCT, OS at 3 years after the allo-HSCT was 36% (95% CI 25.4-51.2).

Prognostic factors for survival after first salvage post auto-HSCT

The results of the univariate analysis for OS are shown in Table 3. OS at 3 years of patients who relapsed after 1 year was 41% (95% CI 31-53) compared with an OS at 3

years of 20% (95% CI 14-24) (**Figure 2**) for those who relapsed less than 1 year after auto-HSCT.

DISCUSSION

Auto-HSCT is the standard of care for those patients with primary refractory or relapsed DLBCL that achieve a chemosensitive status after salvage chemotherapy strategies [5]. Although many patients can be cured with this strategy, a significant proportion relapses or progresses after auto-HSCT. The prognosis of patients who fail auto-HSCT is dismal and effective treatment options in this situation are limited. In addition, patient selection for secondary salvage strategies is challenging, as there are not known factors to predict their outcome. The objective of this retrospective study of the LWP of the EBMT including the largest series of patients analyzed is to shed some light on the outcome of this population.

This study focuses in patients who received “active therapy” for relapse after first auto-HSCT. The main flaw of this study is that, given the inherent nature of the study, treatment was classified in an arbritary decision as ‘palliative’ or ‘active’ by the PIs, after reviewing the data on treatment at relapse, but without any information on the intention of the treating physician. Steroids, radiotherapy or single agent chemotherapy were considered “palliative” options, as there is no evidence that any of these options can provide a cure or even a durable response in this population. In contrast, regimens including platinum or other drugs such as anthracyclines, cytarabine, ifosfamide or gemcitabine that are often part of first or second line for DLBCL and have a significant toxicity to be considered palliative, were considered “active” therapy [15]. Lenalidomide and bendamustine combinations were considered “active” non-intensive combinations as these agents can induce durable remissions in DLBCL patients [16-19].

In our series, patients with DLBCL who relapse after auto-HSCT and can been treated with an active salvage therapy are young, two thirds maintain a good performance status, thereby permitting a variety of active therapies, almost half of the patients respond to salvage therapy, and one third have undergone a second HSCT, most of them an allo-

HSCT. Nevertheless, median survival is short at around 10 months, and most of the patients die of progressive disease.

Although relapse after auto-HSCT is mostly an early event with a median time from auto-HSCT to relapse of 7 months, 35% of the patients in our series relapsed post auto-HSCT after more than one year of being in CR. These results are in line with what has already been published before; in the CORAL trial [8], 75 (30%) out of 255 patients who underwent auto-HSCT as a second line strategy, relapsed after it. Median time to relapse was 7.1 months, and 33% of the global series relapsed after being in CR longer than 1 year. The University of Pennsylvania published a retrospective analysis that included 56 patients with DLBCL relapsing after auto-HSCT [7] showing 20% of relapses occurred more than one year after auto-HSCT. Patients with a more prolonged CR after auto-HSCT constitute a sub-group with a more favorable outcome. In our analysis, OS at 36 months was 41% in patients relapsing beyond a year post auto-HSCT in comparison with 20% in patients with a shorter response after auto-HSCT. This study also shows that those patients with a longer CR after transplant do significantly better with a median OS of 27 months, with a flattening in the curves at around 40%-50% at 2 years [7]. These results support consideration of standard active chemotherapy approaches in this specific subgroup of patients, although no standard treatment strategy has been established for this cohort of patients. In our series 29% of the patients achieved a CR after salvage and 17% a PR. Although several prospective clinical trials have demonstrated the safety and efficacy of new drugs in this setting [16,20,21], most of them do not have an approval by the regulatory agencies in Europe preventing their broader use. In addition their curative potential remains to be determined. Consolidation with a second transplant, especially allo-HSCT with reduced intensity conditioning regimen has been shown to be associated with durable disease control and a beneficial graft versus lymphoma effect [11,12,22]; PFS and OS at 3 years are around 40 to 50% and non-relapse mortality between 20 and 30%. Patients with a prolonged remission after auto-

HSCT, adequate performance status and chemosensitive disease at the time of allo-HSCT have a better outcome after this procedure [12].

On the other hand, patients relapsing less than one year after auto-HSCT have a very poor outcome with an OS at 3 years of 20% in our series; this supports the need to search for additional therapeutic strategies for these patients. In the large international SCHOLAR-1 study, 636 refractory patients with DLBCL were analyzed, including 110 patients who relapsed less than one year after auto-HSCT [23]. Thirty-four percent responded to subsequent therapies with a median survival of 6 months, similar to our results and to results from other studies [7,8]. These observations indicate a significant unmet need for effective therapies, and therefore, these patients should be considered for clinical trials with new targeted drugs or new immunotherapies such as CAR T cells. Recently published results of the pivotal phase II clinical trial ZUMA-1 that included mostly patients with relapsed / refractory DLBCL [13] using axicabtagene ciloleucel, an anti-CD19 CAR T cell construct, showed a CR rate of 54%. With a median follow-up of 15 months, 42% of the patients remain In remission, with 40% continuing to have a CR. The OS at 18 months was 52%. Similarly, the phase II Juliet Trial [14] using tisagenlecleucel (CTL019) in a population of 147 patients with multiply relapsed / refractory aggressive B cell lymphoma, resulted in an overall response rate of 53% with a CR rate of 40%. With a short follow up of the series, the median OS and duration of response was not reached and most patients achieving a CR maintained a response at last follow-up. Of note, in the latter study 50% of the patients with DLBCL treated with CAR T cells had had a previous auto-HSCT. These compelling results might compete with those of allo-HCT or other potential treatment strategies in this relapsed setting. Nevertheless, the number of patients treated with CAR T cells is still quite limited, the follow up is too short to be meaningful for long term outcome, and one must also take into consideration the time needed for CAR T cell production which might be difficult for

timely use of this strategy in some patients. Finally, the enormous economic impact associated with this treatment strategy has to be taken into account.

In conclusion, in this report we describe a large series of patients with DLBCL who relapsed after auto-HSCT and were treated with active therapy. The outcome of patients with a response duration after auto-HSCT is encouraging and suggests that selected patients are candidates for an active treatment with a curative intention. In contrast, the management of patients who relapse in less than one year after auto-HSCT represent an unmet need for effective therapies, and should be considered for CAR T cell therapy or clinical trials. Our results provide a benchmark to compare data of prospective studies conducted in this patient population.

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DISCLOSURE

The authors declare no competing financial interests.

Table 1. Clinical characteristics of 256 patients with DLBCL treated with active therapy for relapse after first auto-HSCT

	n (%)
At diagnosis of DLBCL	
Age in years, median IQR	51 (42-58)
Male gender, n(%)	154 (60%)
Ann Arbor Stage III-IV (n=247), n(%)	183 (74%)
Time from diagnosis to auto-HSCT in months, median (IQR)	10 (6.2-21.6)
At auto-HSCT	
Age at auto HSCT in years, median IQR	52 (43-59)
At relapse after auto-HSCT	
Age in years, median IQR	53 (44-61)
Time from 1st auto-HCT to relapse in months, median (IQR)	7 (3-16)
Relapse ≤1 yr after 1st auto-HCT, n(%)	166 (65%)
Previous chemotherapy lines before 1st auto-HCT, n(%)	
1	78 (30%)
2	128 (50%)
3	38 (15%)
≥4	12 (5%)
Disease status at 1st auto-HSCT (n=253), n(%)	
CR	130 (51%)
PR	79 (31%)
Active disease (SD/PD)	44 (17%)
B symptoms (n=207), n(%)	55 (27%)

Bulky disease > 5 cm (n=194), n(%)	68 (35%)
Karnofsky < 80% (n=233), n(%)	58 (25%)
Elevated LDH (n=203), n(%)	111
IPI (n=159), n(%)	
0-1	63 (40%)
2	42 (26¨%)
3	30 (19%)
4-5	24 (15%)

DLBCL. Diffuse large B cell lymphoma; auto-HSCT. Autologous stem cell transplantation; CR. Complete remission; PR. Partial remission; SD/PD. Stable disease / Progressive disease; IPI. International prognostic index.

Table 2. Salvage therapy at relapse after 1st auto-HSCT.

	n	%
Platinum-containing regimens	134	52
Active intensive combinations (doxorubibin, cytosine arabinoside, ifosfamide, gemcitabine)	97	38
Active non-intensive combinations	25	10

Auto-HSCT. Autologous hematopoietic stem cell transplantation.

Table 3. Univariate analysis for OS after salvage. Variables at relapse after 1st auto-HSCT

	HR	95% CI	p
Age at SCT > 50 years	0.93	0.70-1.24	NS
Male gender	1.09	0.81-1.46	NS
B symptoms	1.33	0.94-1.89	NS
Bulky disease > 5 cm	1.21	0.82-1.70	NS
Karnofsky < 80%	1.69	1.26-2.32	0.002
Elevated LDH	2.08	1.49-2.86	<0.0001
Time from 1st auto-HSCT to relapse > 1 year	0.52	0.38-0.71	<0.0001

Auto-HSCT: Autologous stem cell transplantation; HR: Hazard ratio; CI: Confidence interval; NS: non significant

FIGURE LEGENDS

Figure 1. Criteria for patients to be included in the study

Figure 2. Overall survival of the whole cohort of patients (A) and Overall survival according to the time of relapse after auto-HSCT (B)

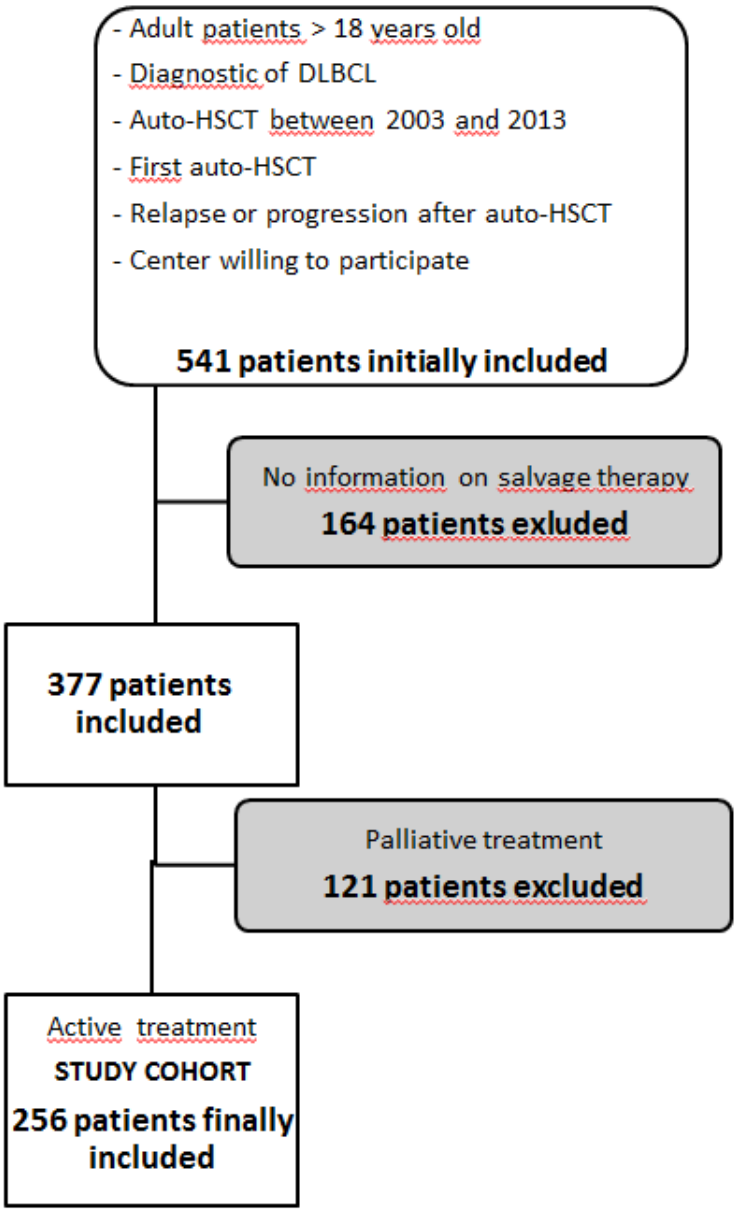

- Adult patients > 18 years old
- Diagnostic of DLBCL
- Auto-HSCT between 2003 and 2013
- First auto-HSCT
- Relapse or progression after auto-HSCT
- Center willing to participate
541 patients initially included
No information on salvage therapy
164 patients exluded
377 patients included
Palliative treatment
121 patients excluded
Active treatment
STUDY COHORT
256 patients finally included

Figure 2 A.

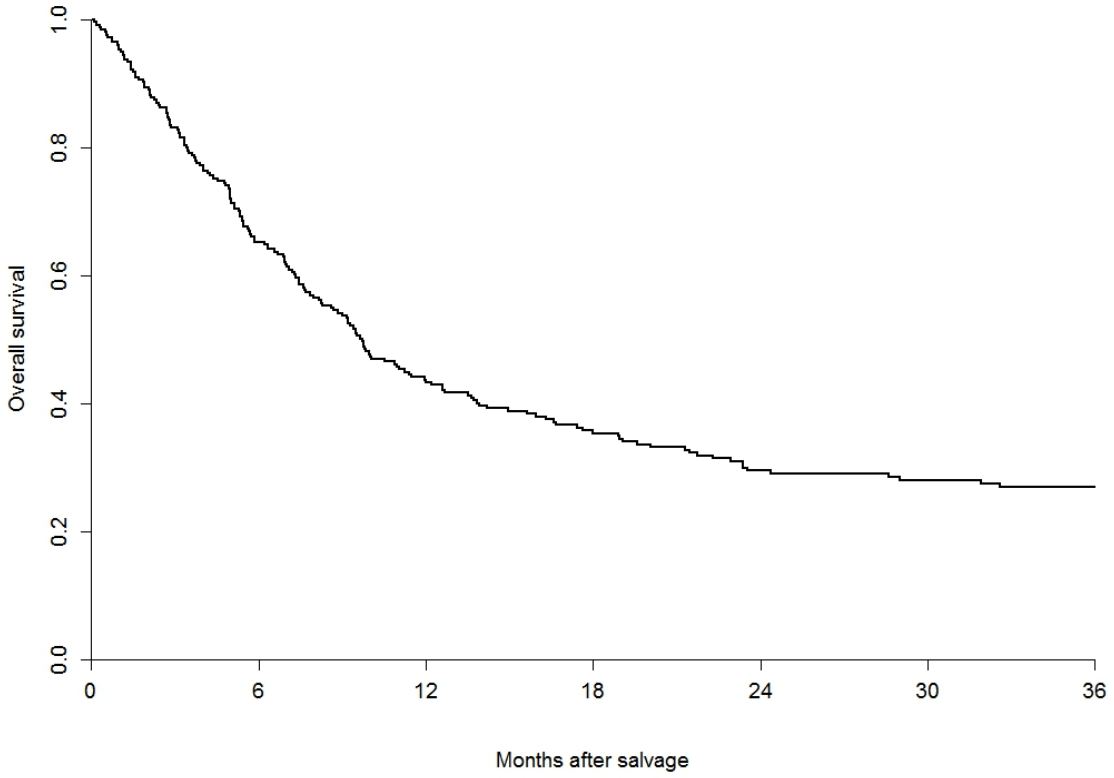
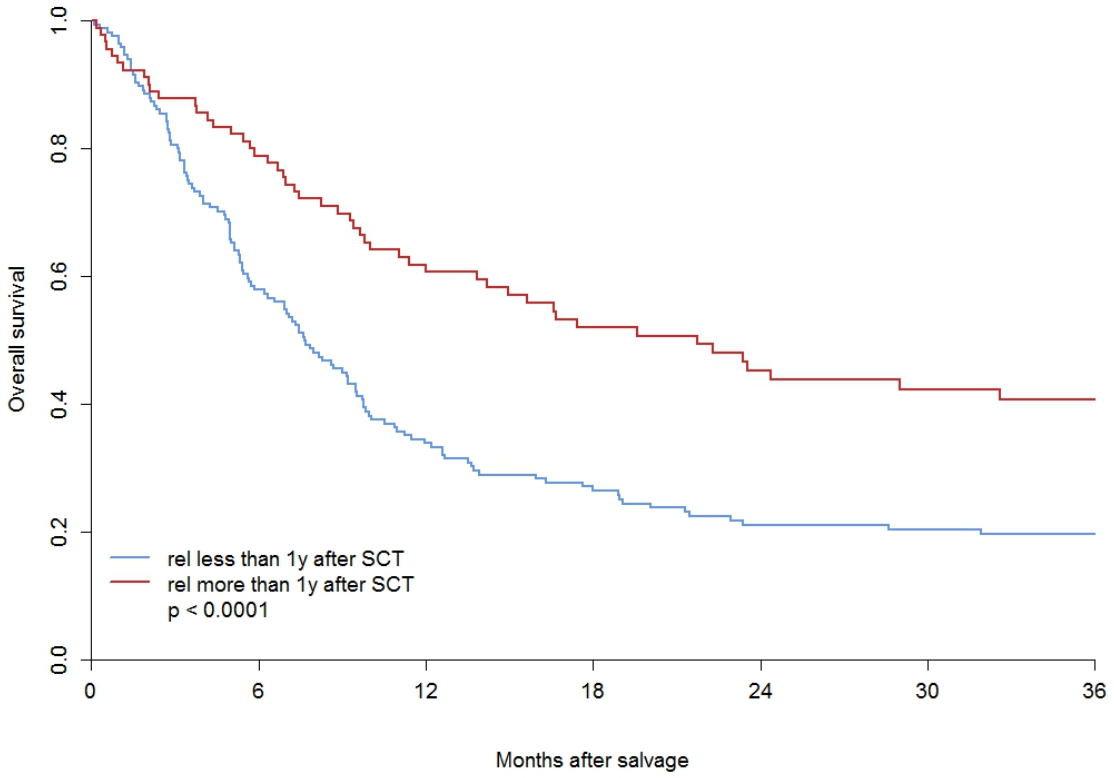

Overall survival
0.0
0.2
0.4
0.6
0.8
1.0
0
6
12
18
24
30
36
Months after salvage

Figure 2 B


Overall survival
0.0
0.2
0.4
0.6
0.8
1.0
0
6
12
18
24
30
36
Months after salvage
rel less than 1y after SCT
rel more than 1y after SCT
p < 0.0001