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ORIGINAL ARTICLE

Second autologous stem cell transplantation for relapsed/refractory Hodgkin lymphoma after a previous autograft: a study of the lymphoma working party of the EBMT

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ABSTRACT

The purpose of this study was to analyze the results of second autologous hematopoietic stem cell transplantation (ASCT2) for patients with relapsed/refractory Hodgkin lymphoma (HL) after a first transplantation (ASCT1). Outcomes for 56 patients receiving an ASCT2 registered in the EBMT database were analyzed. The 4-year cumulative incidences of non-relapse mortality and disease relapse/progression were 5% and 67%, respectively. The 4-year overall survival (OS) and progression-free survival (PFS) were 62% and 28%. In univariate analysis, relapse of HL within 12 months of ASCT1 was associated with a worse OS (35% versus 76%, $p = 0.01$) and PFS (19% versus 29%, $p = 0.059$). Chemosensitivity at ASCT2 predicted better outcomes (4-year OS 72% versus 29%, $p = 0.002$; PFS 31% versus 12%, $p = 0.015$). This series shows that ASCT2 is a safe procedure and a relatively effective option for patients with late relapses after ASCT1 and with chemosensitive disease who are not eligible for an allogeneic transplant.

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Introduction

High-dose chemotherapy followed by autologous stem cell transplantation (ASCT) is currently considered the standard of care for patients with Hodgkin lymphoma (HL) who relapse or fail to respond to the first-line therapy, with sustained remissions after ASCT in a significant proportion of patients [1–9]. However, 40–50% of the patients will present recurrence of the disease. Patients relapsing following ASCT have an overall poor prognosis with an estimated overall survival (OS) of 32% at 5 years according to registry data from the European Society for Blood and Marrow Transplantation (EBMT) [10]. New agents such as brentuximab vedotin or checkpoint inhibitors have recently been approved for the treatment of this population. Although these new drugs seem to prolong the expected median survival following ASCT failure, their efficacy to provide a cure for patients with HL is still unknown [11–13]. Thus, a significant proportion of patients are still considered candidates for a second transplant, usually an allogeneic transplantation (alloSCT) using reduced-intensity conditioning regimens. A second ASCT (ASCT2) has historically been considered as an option only in a small group of patients so the published experience is limited [14–17]. In a retrospective EBMT analysis that analyzed the outcome of 462 patients relapsing/progressing after ASCT, 29% of them were treated with an alloSCT while only 8% received an ASCT2 [10].

We performed a retrospective analysis of the data reported to the EBMT addressing the efficacy and safety of ASCT2 in patients with HL relapsing/progressing after a first ASCT (ASCT1).

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Patients and methods

Data source

EBMT is a voluntary organization comprising more than 600 transplant centers mainly from Europe. Accreditation as a member center requires submission of minimal essential data (MED-A form) from all consecutive patients to a central registry in which patients can be identified by the diagnosis of underlying disease and type of transplantation. MED-A data are annually updated. Additional data regarding specific patient and transplant characteristics were also requested to participant centers. Informed consent for data collection was obtained locally according to regulations applicable at the time of transplantation. Since 1 January 2003, all transplant centers have been required to obtain written informed consent prior to data registration with the EBMT following the Helsinki Declaration 1975.

Patient eligibility

Eligible patients were aged 18 years or older and had undergone an ASCT2 for HL between January 2004 and December 2014. All patients had HL relapse or progression after ASCT1 and received ASCT2. Patients were included in the study independently of the number of therapy lines and the number of relapse episodes between both transplant procedures. Patients receiving tandem ASCT were not eligible. Baseline information, transplantation characteristics, and outcomes after ASCT2 of eligible patients were downloaded from the EBMT database and analyzed.

Study endpoints

Primary objectives of this retrospective study were to determine the overall survival (OS) and progression-free survival (PFS) after ASCT2. Secondary objectives were to determine the cumulative incidence of non-relapse mortality (NRM) and disease relapse, and to describe the time to engraftment after ASCT2. Patient-, disease-, and transplant-related variables associated with these outcomes after ASCT2 were also analyzed.

NRM was defined as the time from ASCT2 to death in the absence of prior relapse/progression. The cumulative incidence of disease progression/relapse was calculated as the time from ASCT2 to relapse/progression. NRM and relapse rate events were considered as competing risks. OS was defined as the time from ASCT2 to death from any cause, and PFS was defined as the time from ASCT2 to relapse/progression or death from any cause.

Statistical analysis

OS and PFS were calculated using the method of Kaplan and Meier. NRM and disease relapse/progression were calculated using cumulative incidence curves to accommodate corresponding competing risks. Univariate analyses were performed using the log-rank-test, Gray's test for competing risk and cause-specific Cox models; due to the small sample size, no multivariate analysis was performed. Analyses were performed using R version 3.5.2 (R Core Team (2018). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

Results

Patient, disease, and transplants characteristics

The baseline patient-, disease- and transplant-related characteristics at ASCT1 and ASCT2 are shown in Table 1. A total of 56 patients receiving ASCT2 for relapsed/progressive HL after ASCT1 were enrolled in this study. The median interval from HL diagnosis to ASCT1 was 17 months (range, 4–135). Seventy-five percent of the patients had received 3 or less chemotherapy lines before ASCT1. No patients were treated with brentuximab vedotin and only one patient received check-point inhibitors before ASCT1. The median time from ASCT1 to relapse or progression was 14 months (0.5–156). Additional information regarding HL characteristics at relapse/progression after ASCT1 was available in some patients: 12/29 (41%) had III-IV stage HL, 12/32 (38%) B symptoms, 2/30 (7%) bulky disease, and 9/33 (27%) extranodal involvement. Only 2 (4%) patients were treated with brentuximab vedotin before ASCT2, and no data were available regarding treatment with check-point inhibitors. Carmustine-based conditioning regimens were used for ASCT1 in 45 (80%) patients, most of them consisting of BEAM (carmustine, etoposide, ara-C, and melphalan) regimen. Preparative regimens for ASCT2 were more heterogeneous (BEAM or similar in 27, 48%; CBV [cyclophosphamide, carmustine and VP-16] or similar in 8, 14%; and others in 21, 37%). Most patients (94.6%) received peripheral blood stem cells. In 20 cases among 35 with available information, ASCT2 was performed using stem cells collected as back-up before ASCT1 (Table 1). Disease status at ASCT2 was complete remission (CR) in 20 (36%) patients, partial

Table 1. Patient, disease, and ASCT1 and ASCT2 characteristics.

Variable	ASCT1	ASCT2
Number of patients	56	56
Sex: male/female	42 (75%)/14 (25%)	
Age at transplant	30 (12–68)	33 (19–71)
Year of transplant (median, range)	2005 (1997–2014)	2008 (2004–2014)
Karnofsky score prior to transplant		
• ≥ 80	46 (92%)	46 (87%)
• Missing	6	3
Disease status at transplant		
• Complete remission	22 (39%)	20 (36%)
• Partial remission	19 (34%)	18 (33%)
• Stable disease	3 (5%)	2 (4%)
• Refractory disease	6 (11%)	8 (15%)
• Untested	1 (2%)	0
• Other[a]	5 (9%)	8 (14%)
Number of chemotherapy lines before transplant (median, range)	2 (1–5)	4 (1–10)
Mediastinal radiotherapy before ASCT	17/36 (47%)	4/34 (12%)
Relapse in pre-irradiated areas	7/32 (22%)	–
Stem cells source		
• Peripheral blood	55 (98%)	53 (95%)
• Bone marrow	0	3 (5%)
• Both	1 (2%)	0
Conditioning regimen		
• BEAM	42 (75%)	27 (48%)
• Other	14 (25%)	29 (52%)
Time from ASCT1 to relapse or progression		
• ≤6 months	18 (32%)	
• 7–12 months	8 (14%)	
• >12 months	30 (54%)	
Time from relapse/progression to ASCT2 in months (median, range)	10 (2–89)	
Time from ASCT1 to ASCT2 in months (median, range)	39 (5–160)	

[a]Categorized in database as: not in relapse, relapse, or unknown.

remission (PR) in 18 (33%), stable disease (SD) in 2 (4%), and progressive disease (PD) in 8 (15%) (Table 1).

Outcomes after ASCT2

The median time to neutrophil ($>0.5 \times 10^9$/L) and platelet ($>20 \times 10^9$/L) recovery after ASCT2 were 11 (IQR 9–12) and 12 (IQR 10–15) days, respectively. One patient died at day 40 after transplant without engraftment.

Toxic pneumonitis after ASCT2 was reported in one patient and no cases of hepatic veno occlusive disease were observed. Best response at day 100 following ASCT2 was CR in 29 (52%) patients and PR in 7 (12%) whereas 3 (5%) had stable disease, and 3 (5%) progressed (9 patients were reported never to be in CR, and in 5 patients data regarding disease response were not available). Twenty-eight (50%) patients are currently alive, with a median follow-up for surviving patients of 97 months (27–177). Two patients developed a secondary neoplasia: acute myeloid leukemia in 1 case, 64 months after ASCT2, and a myelodysplastic syndrome 10 months after the second transplant in the other case. Causes of death were HL progression ($n = 21$, 75%), ASCT2 toxicity ($n = 3$, 11%), secondary neoplasia ($n = 2$, 7%), and unknown ($n = 2$, 7%). The 4-year cumulative incidence of NRM was 5% (95% confidence interval, CI, 1–14%) (Figure 1(A)). The 4-year cumulative incidence of disease relapse/progression was 67% (95% CI 52–77%) (Figure 1(B)). Four-year OS and PFS were 62% (95% CI 51–76%) and 28% (95% CI 18–43%) (Figure 2).

In univariate analysis, chemosensitivity at ASCT2 (CR or PR at the time of transplant) predicted for better outcomes (4-year OS 72% [95% CI 59–89%] versus 29% [95% CI 14–61%], $p = 0.002$; PFS 31% [95% CI 19–50%] versus 12% [95% CI 3–43%], $p = 0.015$; and relapse rate 64% [46–77%] versus 82% [50–95%], $p = 0.023$). In addition, relapse of HL within 12 months of ASCT1 was associated with a worse 4-year OS (35% [95% CI 20–63%] versus 76% [95% CI 63–93%], $p = 0.01$; and PFS (19% [95% CI 9–42%] versus 29% [95% CI 16–51], $p = 0.059$) (Figure 3).

Discussion

Our series is the largest, thus, far describing the outcomes of ASCT2 for patients with relapsed/refractory HL following ASCT1. This registry analysis shows that although ASCT2 is associated with a reasonable low NRM, relapse remains a major issue, especially for patients who relapse in less than 1 year after ASCT1 and/or for those with refractory disease at the time of

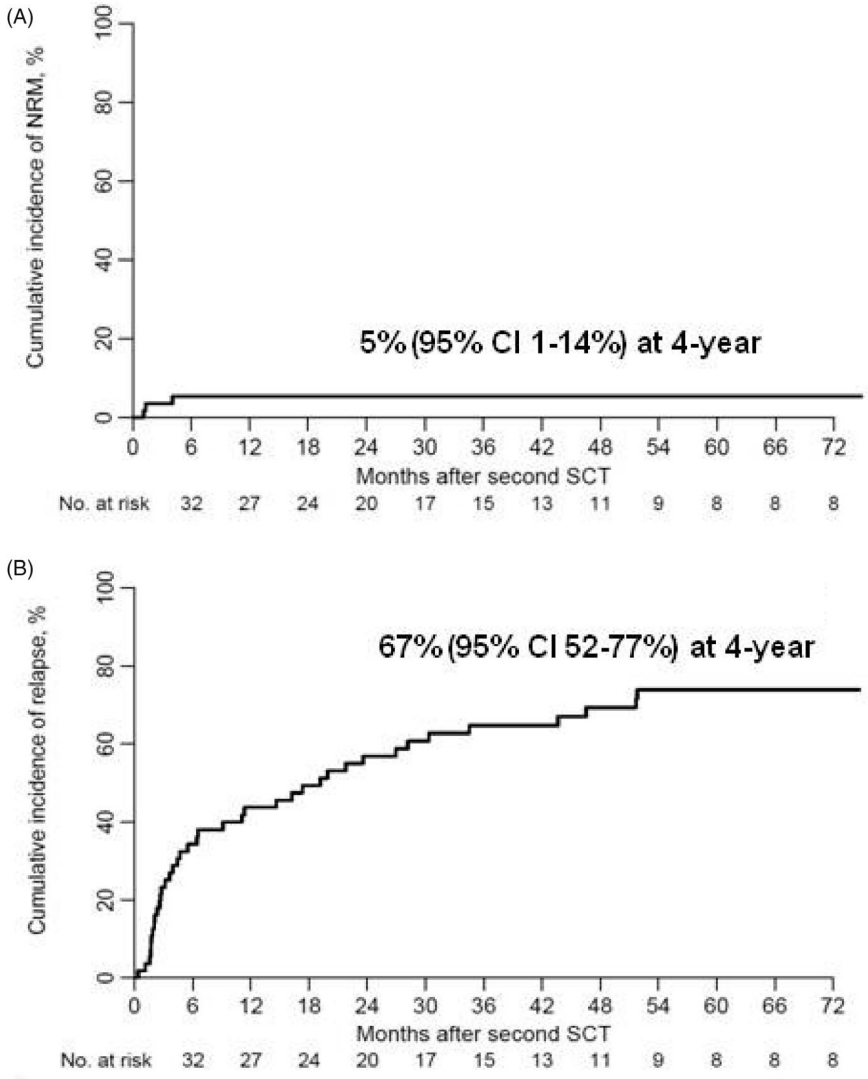


Figure 1. Cumulative incidence of NRM (A) and disease relapse (B) after ASCT2.

second transplant, but it is relatively effective in patients with later relapses and chemosensitive disease.

Limited data are available regarding the use of ASCT2 in patients failing ASCT1. Results of two small studies and a retrospective series from the Center for International Blood and Marrow Transplant Research (CIBMTR) are summarized in Table 2 [14,16,17]. Our study shows lower NRM (5% at 4-year) in comparison to the CIBMTR series (30% at 3-year). This difference could be explained by the period of inclusion of patients that was more recent in our study (2004–2014 for EBMT study versus 1986–2003 for the CIBMTR) [17]. Patient's exposition to older and more aggressive first-line and salvage therapies including mantle radiation could have contributed to a higher toxicity after ASCT2 in the CIBMTR study. The use of TBI-based conditioning regimens (25%) and bone marrow grafts (63%) in CIBMTR study could also have had a role in the increment of NRM.

We observed a high relapse rate after ASCT2 despite the fact that most patients (69%) had chemosensitive disease at the time of transplant. Indeed, progression of HL was the main cause of death following transplantation similarly to that reported in the CIBMTR series [17]. As expected, disease chemosensitivity at ASCT2 was a strong predictor factor of post-transplant outcome. Patients with refractory disease did particularly poorly after ASCT2, with PFS and OS at 4 years of only 12% and 29%, respectively. In comparison, patients with HL in CR/PR at ASCT2 showed a significantly better PFS and OS of 31% and 72%, respectively. These results are quite similar to those reported by CIBMTR with 20% of PFS for chemosensitive disease and 0% for resistant lymphoma. In both studies, time to relapse/progression after ASCT1 was

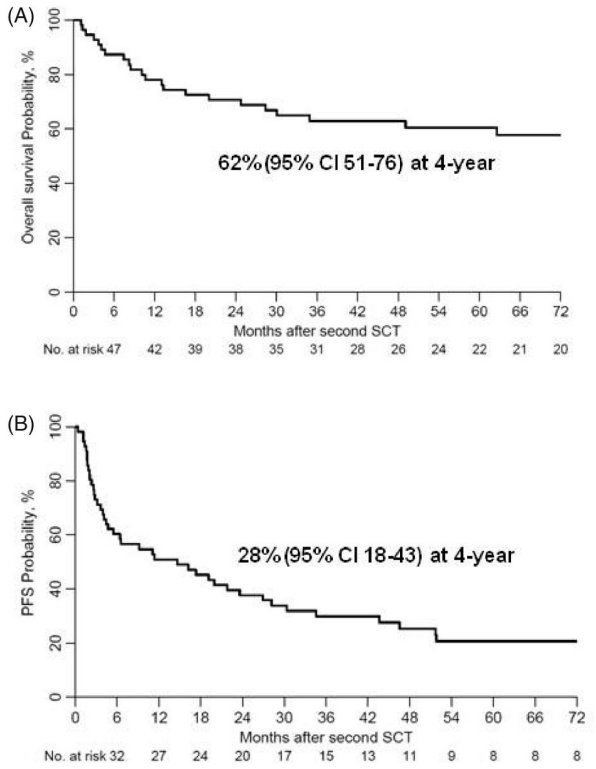
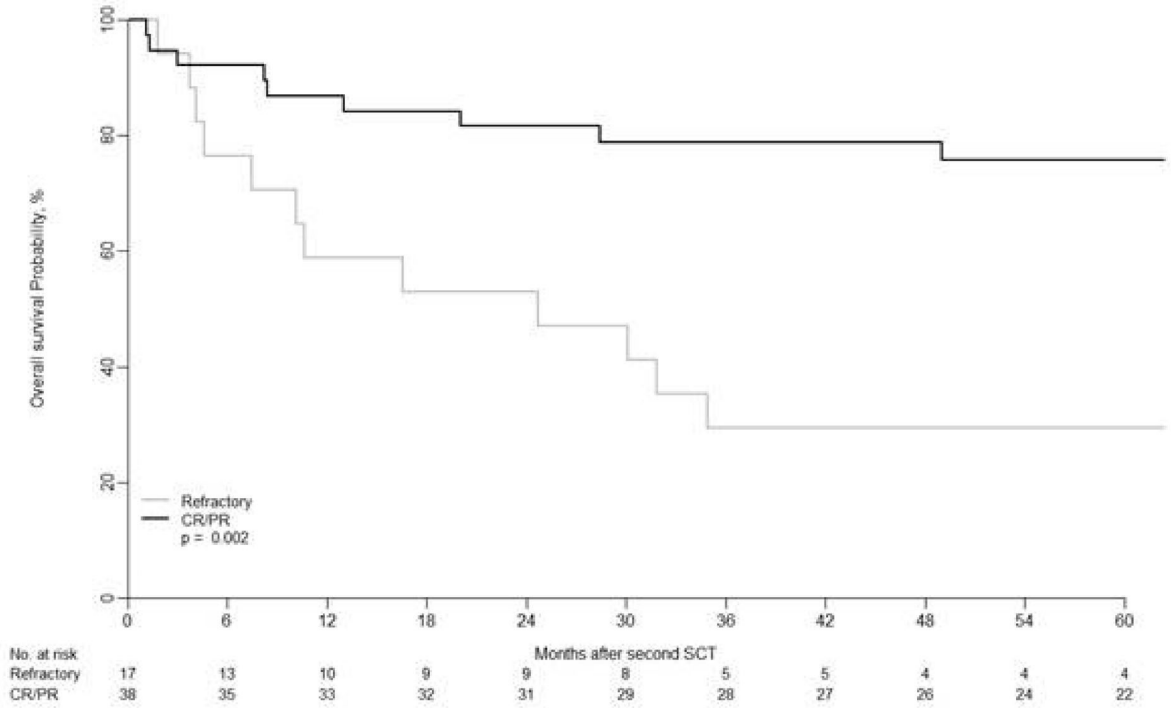


Figure 2. Overall survival and progression-free survival after ASCT2.

also identified as an adverse factor for outcome [17]. In our series, patients relapsing within 12 months of ASCT1 had significantly worse OS (35%) and PSF (19%) in comparison with those relapsing after 12 months of transplant (OS 76% and PFS 29%).

This study has several limitations that are inherent to the retrospective and multicenter nature of the study. We included in the study all patients that received an ASCT2 for R/R HL after first ASCT1 independently of the number of therapy lines and the number of relapse episodes between both transplant procedures. Therefore, we are unable to know what would have been the outcome of ASCT2 after a first disease relapse or progression after ASCT1. Another limitation of this study is the absence of a comparison with a group of patients relapsing/progressing following ASCT1 who did not receive an ASCT2. Therefore, we cannot know if ASCT2 is superior or not to other available therapeutic approaches such as brentuximab vedotin, immune check-point inhibitors, allogeneic stem cell transplantation, chemotherapy alone, or palliative care. The progressive use of new drugs approved for the treatment of HL patients might also have decrease in the number of ASCT2 over the last decades. Based on the available data, allogeneic transplantation, currently considered the standard of care for relapse/progression after ASCT, is associated with an estimated NRM of 10–25% that seems to be higher than that observed in our study after ASCT2 [18–26]. In a recently published EBMT study reporting results of allogeneic transplantation using different types of donors (sibling, unrelated, and haploidentical), OS was quite similar to that reported in the present study (62–71% versus 63%), whereas in the current study ASCT2 was associated with a high relapse rate resulting in a lower PFS (25%) in comparison with allogeneic transplantation (38–45%, depending on the donor type) [26]. Brentuximab vedotin has shown significant efficacy in patients with relapsed/progressive HL after ASCT1 with an OS and PFS at 5 years of 41% and 22%, respectively [11]. However, only 9% of the patients remained in remission at last follow-up. Recent updates follow-up of two phase II trials using check-point inhibitors (nivolumab and pembrolizumab) for relapsed/refractory HL after ASCT, show that responses are frequent (69% and 71.9%, respectively) and durable with a median PFS of 14.7 months and 13.7 months, respectively [12,13]. Unfortunately, the vast majority of responses to check-point inhibitors are partial, and a gradual loss of response over time is common, especially in those who do not achieve CR. It should be noticed that the median follow-up of our study is significantly longer (97 months) in comparison to brentuximab and nivolumab trials. These studies also show that both brentuximab and nivolumab are drugs fairly well tolerated. These targeted therapies may be interest alternatives to a second intensification with reinfusion of autologous stem cells especially for those patients with early relapse.

In summary, our results show that ASCT2 for relapsed/refractory HL after ASCT1 is a safe procedure and a relatively effective option. However, in patients who have not received newer and more effective drugs such as brentuximab vedotin or check-point inhibitors this should be the first option and, in those eligible for allogeneic transplant that should be the objective. ASCT2 could be thus be reserved for patients with late relapses after ASCT1 and with chemo-sensitive disease prior to the second transplant who are not eligible for an allogeneic transplant. It is important to take into consideration that this study describes the results of ASCT2 in a series of patients that precedes the approval of novel and effective alternative agents that have been routinely incorporated into the treatment algorithm for R/R HL. The role of ASCT2 in this new scenario warrants further investigation.



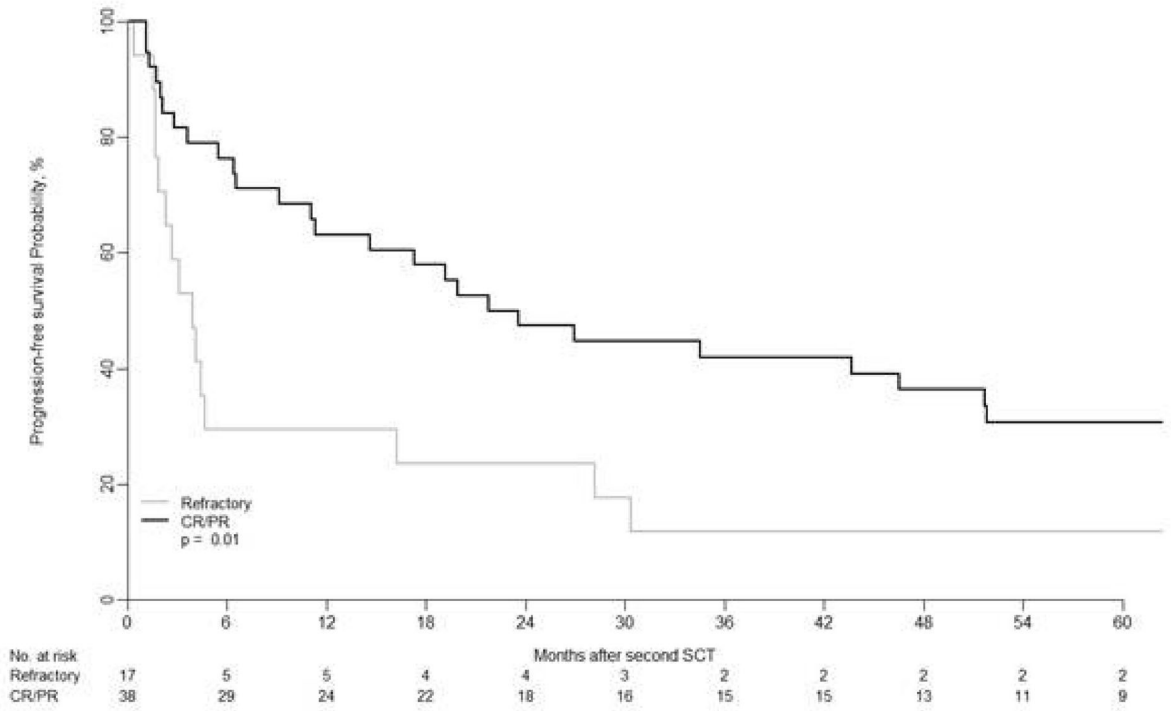


Figure 3. Overall survival and progression-free survival according to the HL status at ASCT2.

Table 2. Summary of the results of ASCT2 for HL.

Series	*N*	Time between ASCT1 and ASCT2	Conditioning regimen	Engraftment (median time after ASCT2)	NRM	Relapse	PFS	OS	Causes of death
Lin et al. [13]	5	Median 66 months	CBV ($n = 4$); Bu-Cy ($n = 1$)	Neutrophils day +10; platelets day +16	2 deaths at 37 and 48 months	No relapses	3 patients alive and disease free at 41, 42 and 155 months	3 patients alive at last follow-up	Pulmonary complications $n = 2$
Thomson et al. [15]	7	–	BEAM ($n = 6$); Thiotepa-Mitoxantrone ($n = 1$)	Neutrophils day +11; platelets day +15	1 death	4 patients	2 patients alive and disease free at 104, and 68 months	3 patients alive at last follow-up	Primary disease, $n = 3$; pulmonary hemorrhage, $n = 1$
Schmith et al, CIBMTR [16][a]	21 HL; 19 NHL	>1 year in 82% patients	BEAM (48%); CBV (17%); TBI-based (20%)	Neutrophils day +11; platelets day +22	36% at 5 years	–	30% at 5 years	30% at 5 years	Primary disease 62%; interstitial pneumonia 3%; infection 3%; organ failure 7%; new malignancy 11%
Martinez et al. [10,26]	56	Median 39 months	BEAM (75%); others (25%)	Neutrophils day +11; platelets day +12	5% at 4 years	67% at 4 years	28% at 4 years	62% at 4 years	Primary disease 75%; ASCT2 toxicity 11%; secondary neoplasia 7%; unknown 7%

HL: Hodgkin lymphoma; NHL: non-Hodgkin's lymphoma.
[a]Results are reported aggregated for NHL and HL.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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