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Original Article

Outcome of Patients with Diffuse Large B-Cell Lymphoma Relapsing after Autologous Transplant before Availability of CAR-T Cell Treatment

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Abstract. ***Introduction*: Autologous stem cell transplantation (ASCT) following high-dose chemotherapy is applied as salvage therapy in patients with relapsed disease or as first-line consolidation in high-risk DLBCL with chemo-sensitive disease. However, the prognosis of relapsing DLBCL post-ASCT remained poor until the availability of CAR-T cell treatment. To appreciate this development, understanding the outcome of these patients in the pre-CAR-T era is essential.**
***Methods*: We retrospectively analyzed 125 consecutive DLBCL patients who underwent HDCT/ASCT.**
***Results*: After a median follow-up of 26 months, OS and PFS were 65% and 55%. Fifty-three patients (42%) had a relapse (32 patients, 60%) or refractory disease (21 patients, 40%) after a median of 3 months post-ASCT. 81% of relapses occurred within the first year post-ASCT with an OS of 19% versus 40% at the last follow-up in patients with later relapses (p=0.0022). Patients with r/r disease after ASCT had inferior OS compared to patients in ongoing remission (23% versus 96%; p<0.0001). Patients relapsing post-ASCT without salvage therapy (n=22) had worse OS than patients with 1-4 subsequent treatment lines (n=31) (OS 0% versus 39%; median OS 3 versus 25 months; p<0.0001). Forty-one (77%) of patients relapsing after ASCT died, 35 of which due to progression.**
***Conclusions*: Additional therapies can extend OS but mostly cannot prevent death in DLBCL relapsing/refractory post-ASCT. This study may serve as a reference to emerging results after CAR-T treatment in this population.**

Keywords: Autologous stem cell transplantation (ASCT); Diffuse large B-cell lymphoma (DLBCL); Chimeric antigen receptor T-cell (CAR-T).

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Introduction. Diffuse large B-cell lymphoma, not otherwise specified (DLBCL, NOS) responds effectively to immunochemotherapy, with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) being the first-line standard.[1–6] In up to 60% of patients, this treatment provides definite complete remission.[7,8] Nevertheless, 30-50% of patients will suffer from relapsed or progressive disease, mostly within the first two years. The current treatment of choice for this patient population is salvage chemotherapy followed by high-dose chemotherapy (HDCT) with peripheral autologous hematopoietic stem cell transplantation (ASCT).[9–12] The most widely used HDCT regimens are BEAM (carmustine, etoposide, cytarabine, melphalan)[11,13], or BeEAM with bendamustine replacing BCNU.[14,15]

Although HDCT followed by ASCT is a successful treatment option for many patients with relapsed DLBCL or high-risk presentation, this treatment is associated with relevant toxicity; importantly, up to 50% of these patients will still relapse or are refractory to this treatment.[16–19] Prognosis of these patients is dismal, and treatment options have been limited so far. Some r/r patients may not receive further interventions after HDCT/ASCT due to lack of response to salvage chemotherapy, poor general condition, or the patient's request, and they undergo palliative treatment. For patients eligible for further therapies, options comprise chemotherapy, immunotherapy, radiotherapy, or combinations of these, in selected cases, allogeneic hematopoietic stem cell transplantation, a second ASCT, or, more recently, CAR (chimeric antigen receptor) T-cell therapy.[11,20] CAR T-cell therapy is a promising new option for patients with DLBCL after two or more therapy lines fail. Recent studies have shown remarkable CR rates of between 40% to 58%.[21–26] On the other hand, CAR T-cell therapy can be associated with relevant specific complications, including cytokine release syndrome (CRS) or CAR T-cell-related encephalopathy syndrome (CRES/ICANS).[21–25,27–29] We performed a retrospective study to describe the outcome of patients with DLBCL after HDCT/ASCT and to determine how high-risk or relapsed DLBCL was managed in clinical practice before the availability of CAR-T cell treatment.

Patients and Methods

Patients. This single-center, non-interventional, retrospective study analyzed the outcome of all consecutive patients with relapsed DLBCL or patients with high-risk presentation who underwent HDCT/ASCT between May 2005 and February 2019 at the University Hospital of Bern, Switzerland. Treatment for DLBCL prior to HDCT/ASCT was applied in various referring centers in Switzerland. Inclusion criteria were the diagnosis of either high-risk DLBCL or relapsed DLBCL (with the subtypes shown in **Table 1**), age of at least 18 years at first diagnosis, and sufficient information on remission status after HDCT with ASCT. Patients with high-risk presentation who were consolidated with ACST after first-line therapy had to have a chemo-sensitive disease and had to achieve partial or complete remission before consolidation.

Patients were divided into two groups depending on their response to HDCT/ASCT. The first group included patients with r/r disease after ASCT. The second group comprised patients in ongoing remission without relapse of DLBCL. All patients gave written informed consent, and this analysis was approved by the local ethics committee of Bern, Switzerland.

Data source. Clinical data for this study were collected from the local electronic patient information system at the University Hospital Bern. Furthermore, information was obtained from the local Management and Resource System for Stem Cell Transplantation (MARCELL), providing specific information on the stem cell transplantation procedures at the University Hospital Bern.

Methods and Definitions. At first diagnosis, patients were staged according to the Ann Arbor classification,[30] and the international prognostic index (IPI) was used for risk stratification.[31] Remission status was determined according to the revised response criteria of the international working group for malignant lymphoma before ASCT, 100 days after ASCT, and at annual follow-up.[32] Response was classified as complete remission (CR), partial remission (PR), stable disease (SD), and progressive disease (PD). CR was defined as complete disappearance of clinical lymphoma evidence and disease-related symptoms. PR was defined as a measurable disease reduction of at least 50% and no occurrence of new lesions. Patients with SD did not fulfill CR/PR or PD criteria. The occurrence of new lesions or the increase of previously reported tumor masses by more than 50% were defined as PD.[32,33]

The primary endpoints were overall survival and progression-free survival. PFS was defined as the time from ASCT until the first evidence of relapse/progression or death from any cause. OS was defined as the time from ASCT until death from any cause.

Statistical analysis. PFS and OS were calculated using the Kaplan-Meier method. Survival differences between subgroups were identified by the log-rank test. Univariate analysis was calculated for the factors: age at first diagnosis, transformed lymphoma vs. *de novo* origin, presence of B-symptoms at first diagnosis, bone marrow infiltration at first diagnosis, radiotherapy administered during first or second-line therapy, the interval between first-line therapy until relapse/progression, the

performance of CD34+ cell positive selection, remission status at ASCT, the interval from ASCT to relapse/progression, number of therapies prior to HDCT/ASCT, and number of further therapies after post-ASCT relapse. P values of <0.05 were assumed to be statistically significant. All data were conducted with GraphPad Prism, and calculations were done by Excel.

Results

Patient characteristics. This study included 125 consecutive patients with DLBCL who received HDCT/ASCT either as first-line consolidation due to high-risk presentation or as salvage therapy for relapsed DLBCL. Clinical characteristics at first diagnosis are summarized in **Table 1**. 63% of the patients were male. The median age at first diagnosis was 58 years (range, 23-76 years). DLBCL NOS (not otherwise specified) was the most common lymphoma subtype (48%). B-symptoms at first diagnosis were present in 44 patients (35%), bone marrow infiltration and central nervous system infiltration were observed in 27 (22%) and 13 patients (10%), respectively.

Transformed lymphoma was present in 23 patients, with 16 (70%) being initially diagnosed with follicular lymphoma, five (22%) with CLL, and one patient (4%) each with marginal zone lymphoma or nodular lymphocyte-predominant Hodgkin lymphoma. 73% of the patients had advanced-stage disease with Ann Arbor stages III (29 pts; 24%) or IV (59 pts; 49%). IPI for risk stratification at first diagnosis was a high-intermediate risk in 35 patients (38%) and high risk in 27 patients (29%).

As described above, patients were distributed into two groups depending on the disease control (relapse or progression) after HDCT/ASCT. Both cohorts were comparable regarding age, gender, lymphoma subtypes, stages, and IPI at first diagnosis (**Table 1**).

Previous therapies before ASCT. Details on the treatment given before HDCT/ASCT are presented in **Table 2**. Patients had a median of two treatment lines before ASCT (range 1-3). Fifty-one patients (41%) received HDCT/ASCT after only one line of therapy due to high-risk presentation, 68 patients (55%) after two,

Table 1. Patient characteristics, lymphoma subtypes, stage and international prognostic index, B-symptoms, CNS infiltration and infiltration of bone marrow at first diagnosis in patients with or without relapsed or refractory disease after ASCT.

Parameter	**All patients n (%)**	**Relapsed patients n (%)**	**Non-relapsed patients n (%)**
Patients, n (%)	125 (100)	53 (42)	72 (58)
Gender			
Male/female (ratio)	79/46 (1.7:1)	32/21 (1.5:1)	47/25 (1.9:1)
Age, years, median (range)			
At first diagnosis	58 (23-76)	58 (24-75)	58 (23-76)
> 60 years	54 (43)	24 (45)	30 (42)
< 60 years	71 (57)	29 (55)	42 (58)
Interval first diagnosis – ASCT, months, median (range)	8 (2-224)	9 (2-81)	7 (2-224)
Lymphoma subtypes, number (%)			
NOS (not otherwise specified)	60 (48)	29 (55)	31 (44)
High-grade BCL (double or triple hits)	12 (10)	4 (8)	8 (11)
Primary mediastinal B cell lymphoma	5 (4)	2 (4)	3 (4)
Primary DLBCL of the CNS	4 (3)	2 (4)	2 (3)
THRLBCL	10 (8)	4 (8)	6 (8)
Intravascular large BCL	6 (5)	2 (4)	4 (6)
Transformed into DLBCL[a]	23 (18)	9 (17)	14 (19)
Others	5 (4)	1 (2)	4 (6)
Stage (Ann-Arbor Classification)[b]			
I	7 (6)	3 (6)	4 (6)
II	26 (21)	10 (19)	16 (23)
III	29 (24)	13 (25)	16 (23)
IV	59 (49)	26 (50)	33 (48)
IPI Risk Score (aaIPI, IPI) [c]			
low risk	15 (16)	4 (12)	11 (19)
low-intermediate risk	15 (16)	6 (18)	9 (15)
high-intermediate risk	35 (38)	14 (42)	21 (36)
high risk	27 (29)	9 (27)	18 (31)
B-symptoms	44 (35)	21 (40)	23 (32)
CNS infiltration	13 (10)	7 (13)	6 (8)
Infiltration of bone marrow	27 (22)	14 (26)	13 (18)

ASCT, autologous stem cell transplantation; THRLBCL, T-cell/histiocyte-rich large B-cell lymphoma; IPI, international prognostic index; CNS, central nervous system. [a] Transformed into DLBCL from: follicular lymphoma (n=16), CLL (n=5), marginal zone lymphoma (n=1), nodular lymphocyte-predominant Hodgkin lymphoma (n=1). [b] Stage not available in 4 patients (3%). [c] (Age-adjusted) International prognostic index not available in 33 patients (26%).

Table 2. Overview on therapies used in one to three previous lines before ASCT.

Parameter	First line n (%)	Second line n (%)	Third line n (%)
Number of patients, n (%)	125 (100)	74 (59)	6 (5)
Relapsed patients, n (%)	53 (100)	40 (75)	4 (8)
Non-relapsed patients, n (%)	72 (100)	34 (47)	2 (3)
Chemotherapies		-	
CHOP	116 (93)	2 (3)	-
DHAP	6 (5)	29 (39)	5 (83)
DHAO	2 (2)	5 (7)	-
ESAP	-	16 (22)	1 (17)
ICE	1 (1)	11 (15)	-
EPOCH	5 (4)	4 (5)	-
MATRIX	3 (2)	4 (5)	-
Bendamustine	3 (2)	2 (3)	-
Others [a]	6 (5)	4 (5)	-
Combined with antibody treatment	117 (94)	70 (95)	5 (83)
Rituximab	117	68	5
Others [b]	0	2	-
Radiotherapy	19 (15)	2 (3)	0 (0)

CHOP cyclophosphamide, doxorubicin, vincristine, prednisone, DHAP dexamethasone, cytarabine, cisplatin, DHAO dexamethasone, high-dose cytarabine, oxaliplatin, ESAP etoposide, methylprednisolone, cytarabine, cisplatin, ICE ifosfamide, carboplatin, etoposide, EPOCH etoposide, vincristine, doxorubicin, cyclophos-phamide, prednisone, MATRIX methotrexate, cytarabine, thiotepa, rituximab. [a] Other chemotherapies used: First line (n=6): unknown (n=1), VCD bortezomib, cyclophosphamide, dexamethasone (n=1), ABVD doxorubicin, bleomycin, vinblastine, dacarbazine (n=2), Hyper-CVAD cyclophosphamide, vincristine, doxorubicin, dexamethasone (n=1), CODOX cyclophosphamide, vincristine, doxorubicin (n=1). Second line (n=4): GDP gemcitabine, dexamethasone, cisplatin (n=2), Hyper-CVAD (n=1), CODOX (n=1). [b] Other adjuvant antibodies used: ofatumumab (n=1), nivolumab (n=1).

Table 3. Characteristics of autologous stem cell transplantation (ASCT) in patients with or without relapsed/ refractory disease after ASCT.

Parameter	All patients n (%)	Relapsed patients n (%)	Non-relapsed patients n (%)
Number of patients, n (%)	125 (100)	53 (42)	72 (58)
Interval first diagnosis – ASCT, months, median (range)	8 (2-224)	9 (2-81)	7 (2-224)
CD34+ mobilization regimens			
DHAO	6 (5)	6 (11)	0 (0)
DHAP	33 (26)	17 (32)	16 (22)
ICE	11 (9)	5 (9)	6 (8)
ESAP	10 (8)	4 (6)	6 (8)
Vinorelbine	51 (41)	16 (30)	35 (49)
Others [a]	14 (11)	5 (9)	9 (13)
Conditioning regimen			
BEAM	42 (34)	16 (30)	26 (36)
BeEAM	74 (59)	33 (62)	41 (57)
Others [b]	9 (7)	4 (8)	5 (7)
Transplanted stem cells, mean, $x10^6$ kg b.w. (range)	3.83 (1.70-7.45)	3.59 (1.96-7.00)	3.99 (1.70-7.45)
Stem cell source [d]			
Peripheral blood	118 (94)	51 (96)	67 (93)
Bone marrow	1 (1)	0 (0)	1 (1)

ASCT autologous stem cell transplantation, HDCT high-dose chemotherapy, DHAO dexamethasone, high-dose cytarabine, oxaliplatin, DHAP dexamethasone, cytarabine, cisplatin, ICE ifosfamide, carboplatin, etoposide, ESAP etoposide, methylprednisolone, cytarabine, cisplatin, BEAM carmustine, etoposide, cytarabine, melphalan, BeEAM bendamustine, etoposide, cytarabine, melphalan. [An] Others: Gemcitabine (n=7), R-IVAC rituximab, ifosfamide, etoposide, high-dose cytarabine (n=2), MATRIX methotrexate, cytarabine, thiotepa, rituximab (n=1), DA-EPOCH-R dose adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab (n=1), CHOP cyclophosphamide, doxorubicin, vincristine, prednisone (n=2), cytarabine and methotrexate (n=1). [b] Other conditioning regimen used: Melphalan (n=1), Carmustine and Thiotepa (n=8). [d] Source of stem cells unknown in 6 patients (5%).

and 6 patients (5%) after three lines of treatment. For first-line treatment, 93% of patients received the CHOP regimen, and 94% of CHOP chemotherapies were combined with rituximab.

High-dose chemotherapy and autologous stem cell transplantation. HDCT/ASCT was performed after a median interval of 8 months from the initial diagnosis. Conditioning regimens in 93% were either the BeEAM (59%) or BEAM (34%). 7% of patients received either melphalan alone or the combination of carmustine and thiotepa as conditioning treatment. Detailed information on HDCT and ASCT is presented in **Table 3**.

Table 4. Therapies patients with relapsed or refractory disease received after ASCT.

Parameter	n (%)
Number of patients with relapsed or refractory disease after ASCT, n (%)	53 (100)
Lines of treatment, median (range)	1 (0-4)
0	22
1	21
≥2	10
Type of therapy	
Chemotherapy	**25**
GemOx	5
MATRIX	2
DHAP	2
Bendamustine	8
ICE	2
Others [a]	6
Additional radiotherapy	6
Additional antibodies [b]	24
2nd ASCT	**3**
Allogeneic SCT	**3**
Radiotherapy (Monotherapy)	**5**
Immunotherapy (Monotherapy) [c]	**5**
Kinase inhibitor (Ibrutinib)	**5**

ASCT autologous stem cell transplantation, GemOx gemcitabine, oxaliplatin, MATRIX methotrexate, cytarabine, thiotepa, rituximab, DHAP dexamethasone, cytarabine, cisplatin, ICE ifosfamide, carboplatin, etoposide. [a] Other chemotherapies used: GDP gemcitabine, dexamethasone, cisplatin (n=2), CHOP cyclophosphamide, doxorubicin, vincristine, prednisone (n=1), EPOCH etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin (n=1), PRIMAIN high-dose methotrexate, rituximab, procarbazine (n=1), MTX methotrexate (n=1). [b] Adjuvant antibodies used: rituximab (n=21), obinutuzumab (n=1), blinatumomab (n=2). [c] Immunotherapies: nivolumab (n=2), brentuximab (n=1), pidilizumab (n=1), blinatumomab (n=1).

Salvage therapy at relapse/progression after HDCT/ASCT. Fifty-three patients (42%) developed relapse or progression after a median interval of 3 months from ASCT (range 1 to 145 months). Thirty-one patients - 58% of all patients with relapse/progression, respectively - received further therapies. Twenty-one patients were treated with one therapy line, and ten patients had two to four treatment lines for relapsing disease after ASCT, with a median of one therapy line (range 0 to 4 lines). 22 patients had no further therapy due to poor general condition or by the patient's wish.

The following further therapies were administered: cytotoxic chemotherapy (25 patients), radiotherapy (five patients), second HDCT/ASCT (three patients), and allogeneic hematopoietic stem cell transplantation (three patients). Three patients received immunotherapy targeting PD-1 (nivolumab: two patients; pidilizumab: one patient), one patient had blinatumomab, five patients were given ibrutinib, and one patient received the antibody-drug conjugate brentuximab vedotin, as listed in **Table 4**.

Outcome. Details on the outcome of the patients after HDCT/ASCT are depicted in **Table 5**. The median follow-up of the entire patient cohort was 26 months. Forty-four patients (35%) died after a median of six months (range 1-64), 35 (80% of the patients) due to disease progression, six due to therapy-related reasons (in five cases due to HDCT associated toxicities, and in one case related to subsequent allogeneic transplantation) and six from other causes.

The median OS of the entire population was 26 months, and the OS rate at the last follow-up was 65% (**Figure 1C**). As expected, patients with r/r disease after ASCT had worse overall survival compared to patients in ongoing remission (OS at last follow-up: 23% vs. 96%; median OS: 9 vs. 38 months; p <0.0001; **Figure 1D**). Progression-free survival (PFS) of the entire cohort at the last follow-up was 55%, with a median duration of response of 19 months (**Figure 1A**). Relapsed or refractory disease occurred in 42% of patients after a median interval of 3 months.

Four factors were identified to be associated with survival rates: interval of relapse from first-line therapy and interval from HDCT/ASCT, number of therapies prior to HDCT/ASCT, and the number of treatment lines after post-ASCT relapse. 38% of patients showed an early relapse after first-line therapy, defined as relapsed disease or progression within the first year. These patients had inferior OS and PFS compared to patients who relapsed after 12 months or later (OS rate at 26 months: 48% vs. 75%, p = 0.0008; PFS rate: 33% vs. 69%, p < 0.0001; **Figure 3A/B**).

When only patients with r/r disease (n=53) following HDCT/ASCT were considered, early relapse or progression within the first 12 months after ASCT occurred in 81% of these patients. 19% of the patients had a late-onset relapse (an occurrence of relapse ≥ 12 months after ASCT). Patients with early relapse or progression had lower OS than patients with late onset of relapse post-ASCT (OS rate at 26 months: 19% vs. 40%, p= 0.0009, **Figure 3D**).

Table 5. Outcome of patients with or without relapsed or refractory disease after ASCT. Median follow up, overall survival, progression-free survival, state of remission, relapse and death.

Parameter	All patients n (%)	Relapsed patients n (%)	Non-relapsed patients n (%)
Number of patients n (%)	125 (100)	53 (42)	72 (58)
Follow up, months, median (range)	26 (1-174)	9 (1-174)	38 (3-107)
OS, months, median (range)	26 (1-174)	9 (1-174)	38 (3-107)
PFS, months, median (range)	19 (1-145)	3 (1-145)	38 (3-107)
State of remission prior to ASCT (day 0)			
CR	35 (28)	10 (19)	25 (35)
PR	83 (66)	39 (74)	44 (61)
SD	2 (2)	1 (2)	1 (1)
PD	5 (4)	3 (6)	2 (3)
State of remission after ASCT (day +100)			
CR	79 (63)	21 (40)	58 (81)
PR	25 (20)	11 (21)	14 (19)
SD	0 (0)	0 (0)	0 (0)
PD	11 (9)	11 (21)	0 (0)
State of remission at last follow-up			
CR	74 (59)	5 (9)	69 (96)
PR	3 (2)	3 (6)	0 (0)
SD	3 (2)	3 (6)	0 (0)
PD	1 (1)	1 (2)	0 (0)
Relapse after ASCT, n (%)	53 (42)	53 (100)	0 (0)
Median time ASCT – relapse, months (range)		3 (1-145)	
Early relapse, n (%)		43 (81)	
Late relapse, n (%)		10 (19)	
Death, n (%)	44 (35)	41 (77)	3 (4)
Interval from ASCT, months, median (range)	6 (1-64)	6 (1-64)	6 (3-24)
Due to progression, n	35	35	0
Related to therapy, n	6	6	0
Other causes, n [a]	3	0	3

OS overall survival, *PFS* progression-free survival, *CR* complete remission, *PR* partial remission, *SD* stable disease, *PD* progressive disease.
[a] Other causes: pneumonia (n=1), intracranial hemorrhage (n=1), infection of the CNS (n=1).

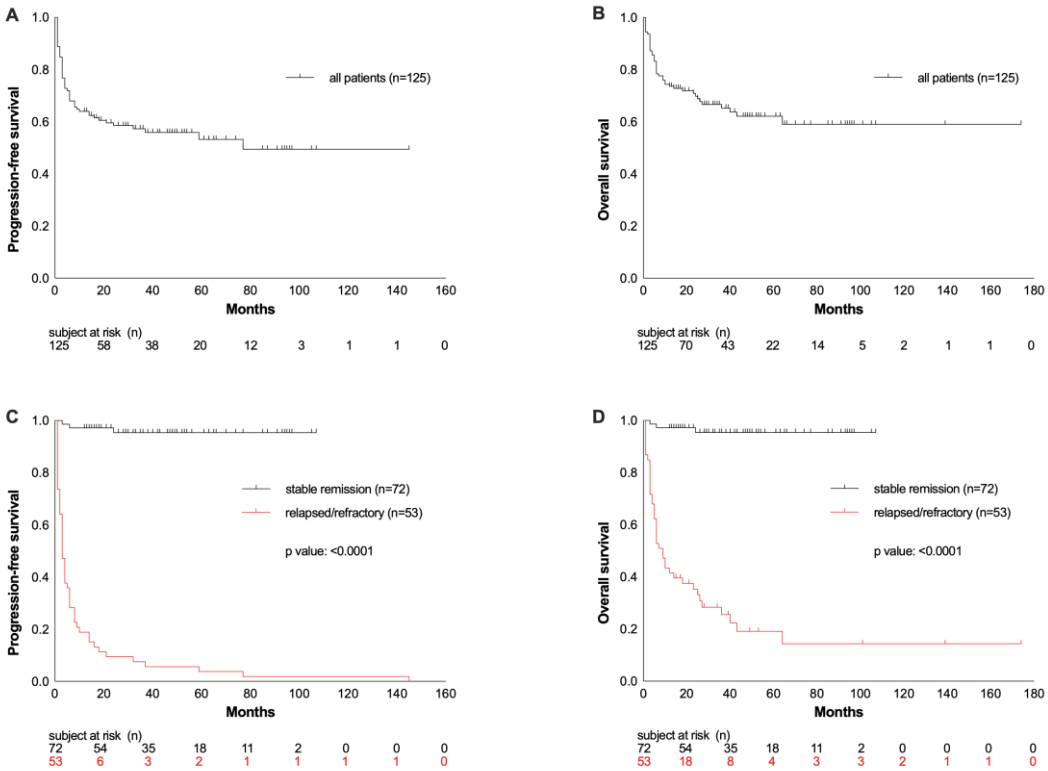

Figure 1. Progression-free survival (PFS) and overall survival (OS) from ACST represented as the whole cohort of patients (**A** and **B**) and compared according to their response to ASCT (**C** and **D**).

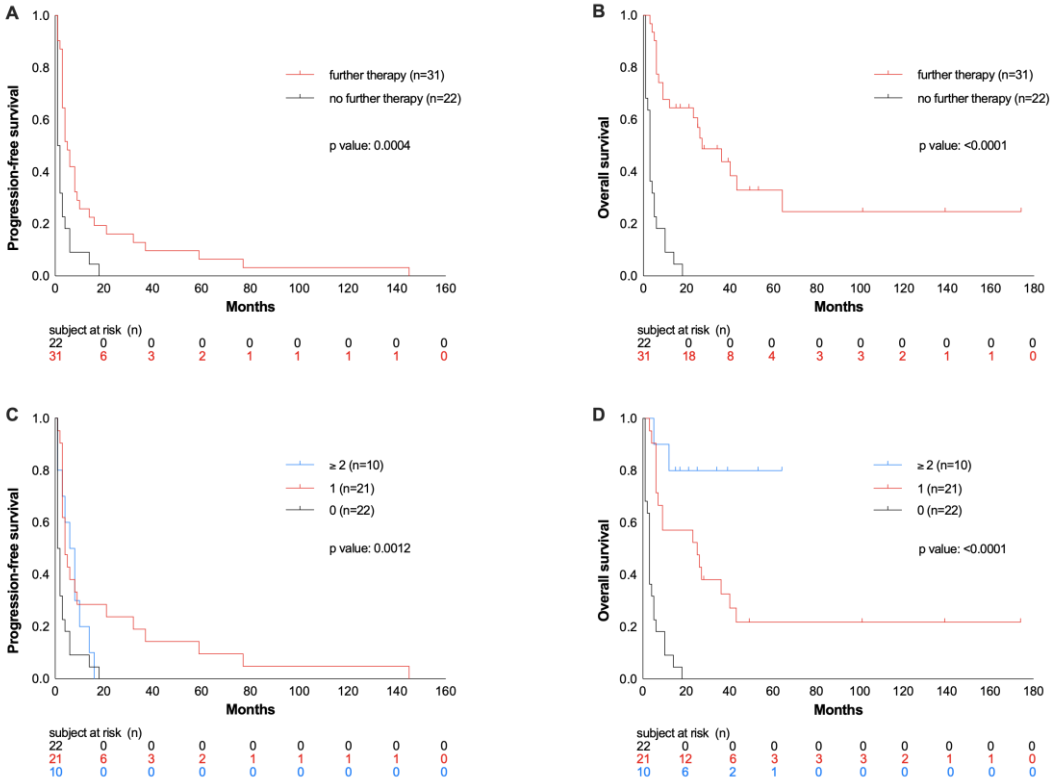

Figure 2. Progression-free survival (PFS) and overall survival (OS) from ASCT in patients with relapsed or refractory disease after ASCT depending on receiving further therapies or not (**A** and **B**) and on number on subsequent therapy lines (**C** and **D**).

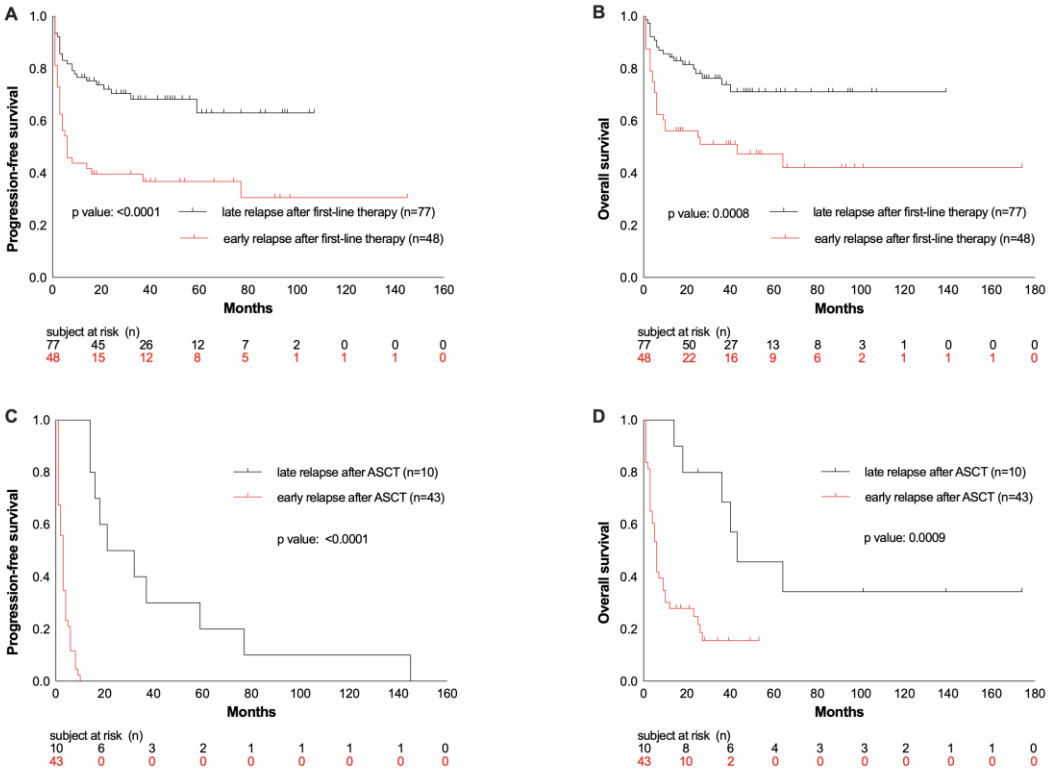

Figure 3. PFS and OS from ASCT depending on the time of relapse after first-line therapy (**A** and **B**) or after ASCT (**C** and **D**).

Comparing the patients' outcome regarding the number of therapies prior to HDCT/ ASCT, a significant benefit was observed in those patients who received HDCT/ASCT after the first-line therapy because of high-risk presentation (n= 51), compared to those patients who had two to three lines of treatment prior to HDCT/ASCT (OS rate at 26 months: 78% vs. 55%, p= 0.0161; PFS rate: 75% vs. 42%, p= 0.0054; **Figure 4 A/B**).

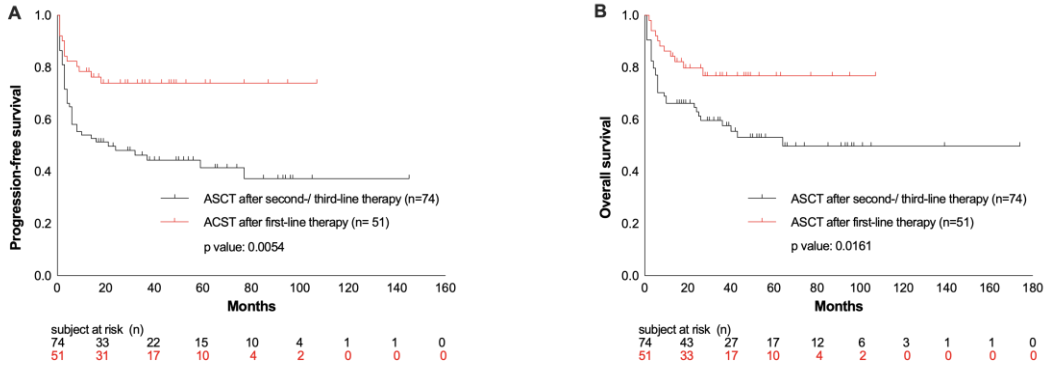

Figure 4. PFS and OS from ASCT depending on number of therapy lines prior to HDCT/ACST (**A** and **B**).

Considering all patients with r/r disease following HDCT/ASCT, the OS rate was only 23% after a median follow-up of 26 months after ASCT. Patients who received no other therapy despite relapse/progression after ASCT due to poor general condition or according to the patient's wish had an even worse outcome compared to patients with additional treatment line(s) in this situation (OS rate at 26 months 0% vs. 39%, p >0.0001, **Figure 2A**). 42% of patients received no further therapy, 40% were treated with one, and 19% with two or more therapy lines, corresponding to OS rates of 0% vs. 24% vs. 70% (p> 0.0001; **Figure 2B**). Thus, in relapsed patients, the OS was longer with an increasing number of therapy lines.

No differences were detected in OS and PFS rates of specific subsets when data were adjusted for the following variables: *de novo* versus transformed lymphoma (OS p=0.7369; PFS p=0.7909), age higher/lower than 60 years (OS p= 0.3617; PFS p= 0.2655), B-symptoms present at first diagnosis yes/no (OS p=0.9446; PFS p=0.7619), bone marrow infiltration present at first diagnosis yes/no (OS p=0.6139; PFS p=0.3870), radiotherapy administered before ASCT yes/no (OS p=0.4674; PFS p=0.8150), and CR at ASCT yes/no (OS p=0.4271; PFS p=0.1398) (**Supplementary material, Figure S1**).

Discussion. Considering the introduction of CAR-T cell therapies for aggressive lymphatic malignancies in Europe and elsewhere,[24,25] we aimed to further characterize the outcomes of patients with DLBCL with a specific focus on those with failure after HDCT/ASCT. We retrospectively investigated a cohort of 125 patients with DLBCL treated with HDCT/ASCT in a single academic/ tertiary center and studied, in particular, the subset of patients who relapsed or developed progression following HDCT/ASCT and who could have benefited from CAR-T therapy, had it then been available.

Confirming reports by others, the present study demonstrates that HDCT, followed by ASCT, provides excellent long-term outcomes in patients with relapsed or refractory DLBCL, achieving stable remission after this salvage therapy option.[9,34,35] In our analysis comprising 125 recipients of HDCT/ASCT due to relapsed DLBCL or high-risk presentation, the ORR was 61% for the total cohort. That 55% of patients in ongoing remission following HDCT/ASCT showed encouraging OS and PFS of 96% with a median duration of 38 months.

In contrast, the prognosis for patients with r/r disease after HDCT/ASCT is poor, especially in those with characteristics such as high IPI or early relapse within 12 months following ASCT.[11,34] In our study, 42% of patients developed relapses or showed progression after HDCT/ASCT. Although 58% of these patients with failure of HDCT/ASCT received other therapeutic approaches, 77% rapidly died after a median interval of 6 months, mostly due to lymphoma progression. Likewise, in the CORAL study, 29% of patients with r/r DLBCL after ASCT had poor survival, with a median OS of 10 months and a 1-year OS of 39.1%.[35]

We evaluated the impact of various parameters on the outcomes of our HDCT/ASCT cohort. Significant impact on survival could only be verified for the duration of the response to first-line therapy, the duration of response after HDCT/ASCT, the number of therapies prior to HDCT/ASCT, and the number of subsequent therapies after post-ASCT relapse. We documented a median interval to progression following ASCT of only 3 months, and 81% of relapses occurred within 12 months after ASCT, demonstrating that DLBCL relapses are associated with rapid kinetics, early manifesting after HDCT/ASCT. Furthermore, the OS rate was only 19% in patients with early relapses (<12 months) post-ASCT, as compared to late relapses (≥12 months after ASCT) with an OS rate of 40%. These results correspond with previous studies demonstrating early relapses following ASCT in 65-80% of patients, associated with a significantly worse OS compared to later time points of relapse.[12,36] Other parameters such as the histopathological origin (transformed vs. de novo DLBCL)[37–41] and CD34+ selection[42–45] had no significant impact on the prognosis of the recipients of HDCT/ASCT in our cohort.

Treatment options for patients with r/r DLBCL following ASCT were so far limited. Allogeneic stem cell transplantation may provide a certain graft versus

lymphoma effect.[46–48] However, only a few DLBCL patients are, in fact, candidates for this approach due to its high transplant-related mortality and high relapse rates. Only three patients in our cohort received an allogeneic SCT, which is representative of the limited use of this option for r/r DLBCL patients.

CAR-T cell therapies, recently introduced, offer patients with r/r DLBCL a promising new option with CR rates of up to 58%.[24,49,50] In several studies, ORR of 52-85% with 40-58% CR rates were achieved by CAR-T cell therapy in patients with r/r DLBCL.[21,24–26,51,52] However, long-term outcomes will still be awaited in the next decades.

In addition, novel immunotherapies such as polatuzumab vedotin,[53] tafasitamab,[54] glofitamab, or mosunetuzumab are additional promising new options for DLBCL patients ineligible for HDCT/ASCT or for those whom CAR-T therapy is no option due to its toxicity, or due to its logistic or financial obstacles.

An obvious limitation of our study is its retrospective single-center design covering a large timespan, including various DLBCL subtypes, heterogeneity in conditioning regimen, and inevitable lack of some data in a few patients. Nevertheless, our study demonstrates the adverse prognosis of DLBCL patients after HDCT/ASCT failure and the limited efficacy of subsequent therapeutic approaches, including a second HDCT/ASCT, allogeneic SCT, radiation, cytotoxic treatment, and traditional monoclonal antibody therapies. Our study emphasizes the urgent need to make CAR-T cell therapies available to all patients with r/r DLBCL following HDCT/ASCT failure.[21]

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