Autologous stem cell transplant in fit patients with refractory or early relapsed diffuse large B-cell lymphoma that responded to salvage chemotherapy

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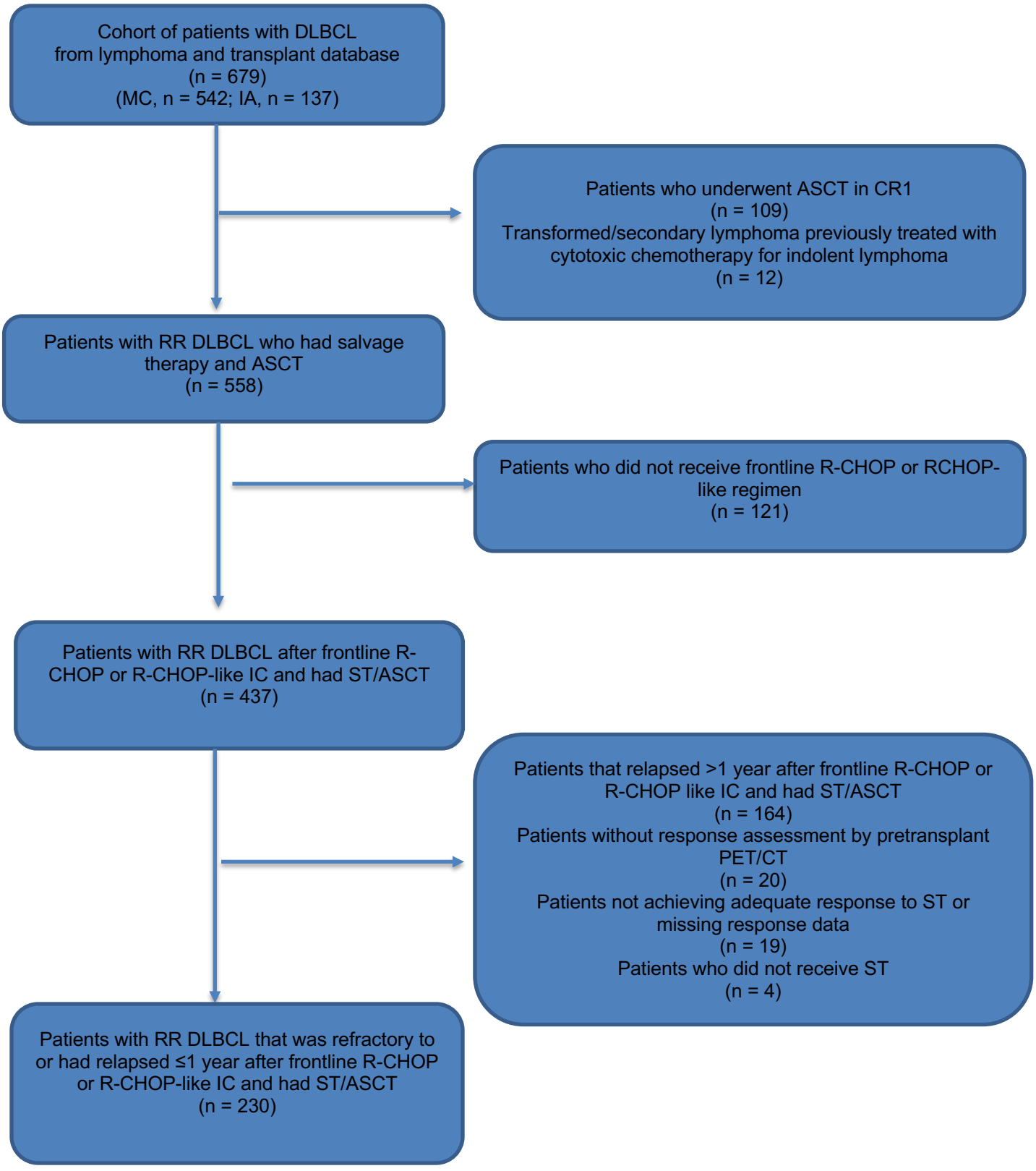
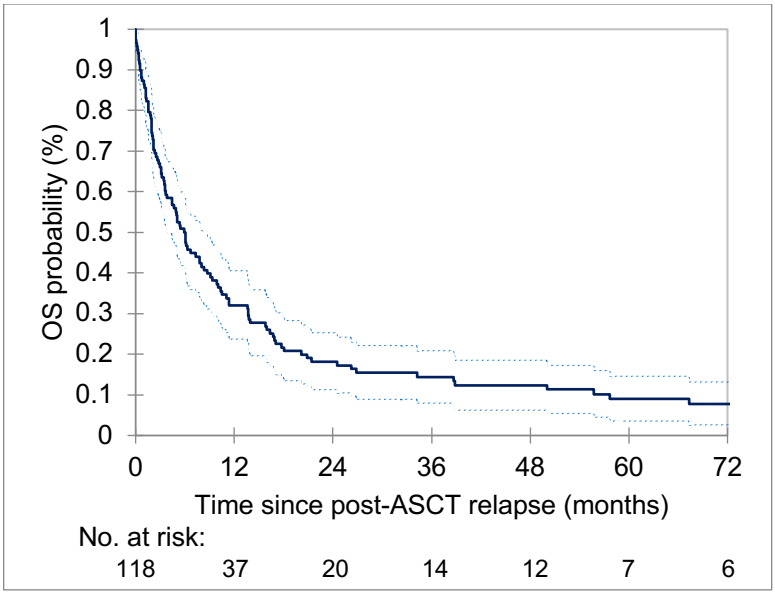
Abstract

Chimeric antigen receptor T-cell therapy is the new standard of care in fit patients with refractory or early relapsed diffuse large B-cell lymphoma (DLBCL). However, there may still be a role for salvage chemotherapy (ST) and autologous stem cell transplant (ASCT) in certain circumstances (e.g., lack of resources for chimeric antigen receptor T-cell therapy, chemosensitive relapses). We retrospectively studied 230 patients with refractory or early relapsed DLBCL who underwent ST and ASCT. The median line of ST was one (range, 1-3). Best response before ASCT was complete response in 106 (46%) and partial response in 124 (54%) patients. The median follow-up after ASCT was 89.4 months. The median progression-free (PFS) and overall survival (OS) were 16.1 and 43.3 months, respectively. Patients relapsing between 6 to 12 months after frontline therapy had a numerically better median PFS (29.6 months) and OS (88.5 months). Patients who required one line of ST, compared to those requiring more than one line, had a better median PFS (37.9 *vs*. 3.9 months; P=0.0005) and OS (68.3 *vs*. 12.0 months; P=0.0005). Patients who achieved complete response had a better median PFS (71.1 *vs*. 6.3 months; P<0.0001) and OS (110.3 *vs*. 18.9 months; P<0.0001) than those in partial response. Patients who achieved complete response after one line of ST had the most favorable median PFS (88.5 months) and OS (117.2 months). Post-ASCT survival outcomes of patients with refractory or early relapsed DLBCL appeared reasonable and were particularly favorable in those who required only one line of ST to achieve complete response before ASCT, highlighting the role of this procedure in select patients with chemosensitive disease.

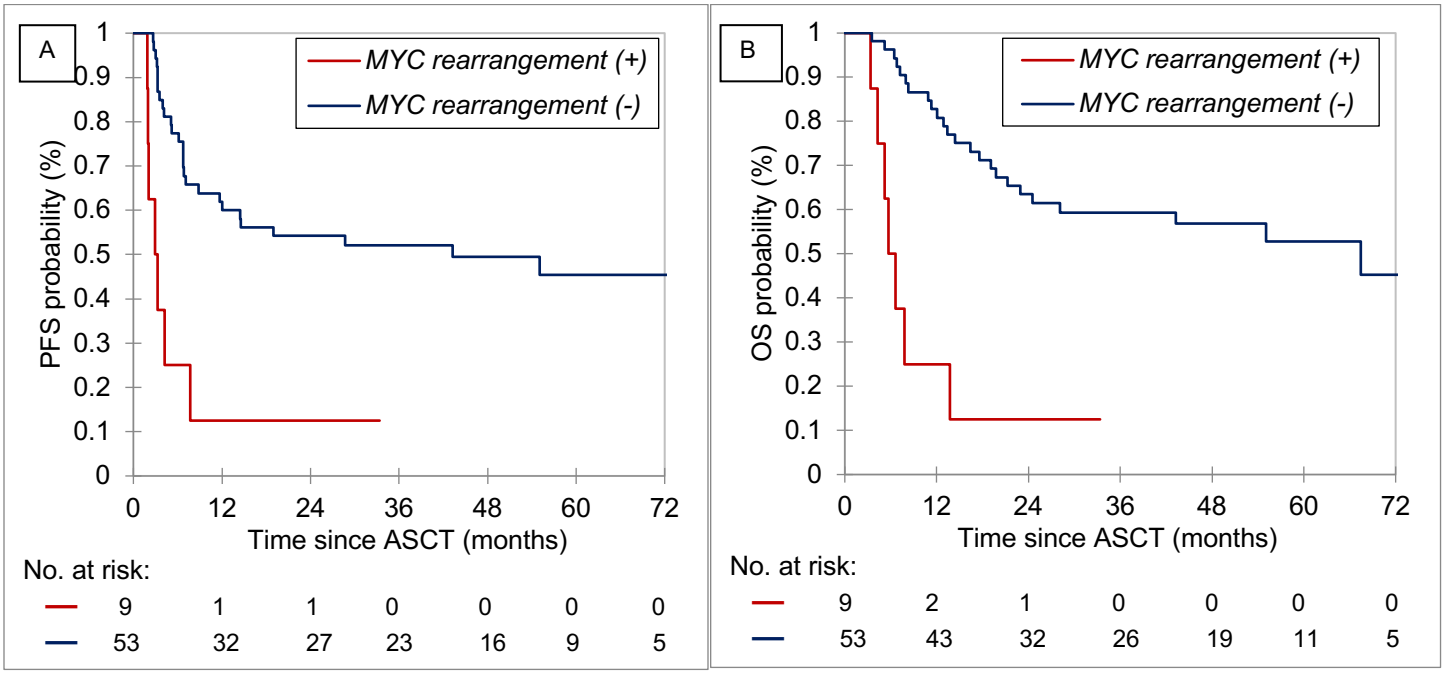
Supplementary Figure 1. Description of study patient selection



Abbreviations: DLBCL, diffuse large B-cell lymphoma; MC, Mayo Clinic; IA, University of Iowa; CR, complete response; RR, relapsed or refractory; ASCT, autologous stem cell transplant; IC, immunochemotherapy; ST, salvage chemotherapy; PET/CT, positron emission tomography-computed tomography



Supplementary Figure 2. OS of study patients after post-ASCT relapse
Abbreviations: OS, overall survival; ASCT, autologous stem cell transplant



Supplementary Figure 3. Post-ASCT outcomes according to *MYC* rearrangement status: (A) PFS and (B) OS
Abbreviations: PFS, progression-free survival; OS, overall survival; ASCT, autologous stem cell transplant

Supplementary Table 1. Characteristics of patients with DLBCL at initial diagnosis in MC and IA transplant database treated in the rituximab era

Baseline Characteristics	(n = 230)	%
Age at diagnosis, years		
≤60	128	56
>60	102	44
Sex		
Male	149	65
Female	81	35
ECOG PS scale		
≤1	201	91
>1	21	9
Missing	8	---
LDH		
Normal	35	21
Elevated	135	79
Missing	60	---
Extranodal sites		
≤1	167	74
>1	59	26
Missing	4	---
Ann Arbor Stage		
I-II	41	18
III-IV	189	82
IPI risk classification		
Low	22	13
Low-intermediate	57	34
High-intermediate	67	40
High	23	14
Missing/incomplete evaluation	61	---
Cell of origin		
GCB	73	60
Non-GCB	49	40
Missing/not performed	108	---
***MYC* rearrangement status**		
Present*	9	15
Absent	53	85
Missing/not performed	168	---

*4 patients had *MYC* and *BCL2* rearrangements; 3 had *MYC, BCL2,* and *BCL6* rearrangements; 1 had *MYC* and *BCL6* rearrangements; and 1 had *MYC* rearrangement.
Abbreviations: DLBCL, diffuse large B-cell lymphoma; MC, Mayo Clinic; IA, University of Iowa; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; IPI, international prognostic index; GCB, germinal center B-cell

Supplementary Table 2. Treatment pattern and response to therapy in study patients with RR DLBCL

	n=230	%
First line salvage regimen		
Platinum or high dose cytarabine containing chemotherapy[1]	201	87
High dose methotrexate based chemotherapy[2]	26	11
Other chemotherapy[3]	3	1
Lines of ST		
1	178	77
>1	52	23
Response to ST		
CR	106	46
PR	124	54
Conditioning Regimen		
BEAM	213	93
Other regimens[††]	17	7
Disease Status Post-ASCT		
CR	123	56
Non-CR	96	44
Radiation post-ASCT (consolidation)		
Yes	18	8
No	212	92

[1] (R-)ICE, rituximab, ifosfamide, carboplatin, etoposide; (R-)DHAP, rituximab, dexamethasone, Ara-C, cisplatin; RGDP, rituximab, gemcitabine, dexamethasone, cisplatin; ROAD, rituximab, oxaliplatin, Ara-C, dexamethasone; (R-)ESHAP, rituximab, etoposide, methylprednisone, Ara-C, cisplatin; and RGemOx, rituximab, gemcitabine, oxaliplatin

[2]methotrexate with or without rituximab and/or temozolomide

[3]R-CDE, rituximab, cyclophosphamide, doxorubicin, etoposide; rituximab, mitoxantrone, and fludarabine; R-EPOCH; rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin

[††] BCNU and Thiotepa; BVAC, BCNU, etoposide, Ara-C, cyclophosphamide; and BEC, BCNU, etoposide, and cyclophosphamide

Abbreviations: RR, relapsed or refractory; DLBCL, diffuse large B-cell lymphoma; ST, salvage chemotherapy; CR, complete response; PR, partial response; BEAM, BCNU, etoposide, Ara-C, and melphalan; and ASCT, autologous stem cell transplant

Supplementary Table 3. Post-ASCT outcomes at 12 months, 24 months, and 60 months

	At 12 months (95% CI)	At 24 months (95% CI)	At 60 months (95% CI)
PFS	53% (47–60)	47% (41–54)	41% (34–47),
OS	68% (61–74)	57% (50–63)	48% (41–55),
DOR	78% (70–85)	72% (64–80)	61% (52–70),
Relapse	43.4% (37.5–50.2)	47.8% (41.8–54.6)	52.0% (45.8–58.9)
Nonrelapse mortality	3.9% (2.0–7.4)	4.8% (2.7–8.5)	7.3% (4.5–11.7)
Causes of death			
Lymphoma	28.5% (23.2–35.0)	37.8% (32.0–44.7)	42.7% (36.7–49.7)
Treatment-related deaths	2.1% (0.9–5.2)	3.1% (1.5–6.4)	3.6% (1.8–7.1)
Other causes	1.3% (0.4–4.1)	1.8% (0.7–4.7)	3.8% (1.9–7.5)
Unknown	0.9% (0.2–3.5)	0.9% (0.2–3.5)	1.8% (0.7–4.8)

Abbreviations: ASCT, autologous stem cell transplant; CI, confidence interval; PFS, progression-free survival; OS, overall survival; DOR, duration of response

Supplementary Table 4. Subsequent first line treatment after post-ASCT relapse

Subsequent first line treatment after post-ASCT relapse	DLBCL	
	N=118	%
Systemic chemotherapy	25	21
CNS directed chemotherapy	9	8
Cellular therapy	2	2
Radiation/surgery	21	18
Lenalidomide containing therapy	5	4
Others	25	21
Radioimmunotherapy/single agent rituximab	5	4
Palliative care	19	16
Unknown	7	6

Abbreviation used: ASCT, autologous stem cell transplant; DLBCL, diffuse large B-cell lymphoma; CNS, central nervous system.
Systemic chemotherapy: rituximab, gemcitabine, cisplatin, and dexamethasone (R-GDP); rituximab, ifosfamide, carboplatin, and etoposide (RICE); rituximab, gemcitabine, vinorelbine, and prednisone (R-GVP); rituximab, dexamethasone, cytarabine, and cisplatin (R-DHAP); cyclophosphamide, doxorubicin, etoposide, bleomycin, vincristine, methotrexate, and prednisone (ProMACE CytaBOM); nitrogen mustard and solumedrol; cyclophosphamide, fludarabine, and rituximab; bendamustine and rituximab (BR); rituximab, gemcitabine, and oxaliplatin (R-GemOx), rituximab, etoposide, methylprednisone, high dose cytarabine, and cisplatin (R-ESHAP); dose-adjusted rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (EPOCH-R); and polatuzumab vedotin plus BR
CNS directed chemotherapy: methotrexate, temozolomide, and rituximab (MTR)
Cellular therapy: chimeric antigen receptor T-cell therapy and allogeneic stem cell transplant
Others: everolimus, sorafenib, panobinostat, nivolumab, pembrolizumab, ipililumab, anti-TRAIL antibody, acalabrutinib, ruxolitinib, pixantrone, and fostamatinib

Supplementary Table 5. Causes of Death

Causes	N = 136
Lymphoma	101
Treatment-related deaths[†]	11
Other causes[‡]	13
Unknown causes	11

[†]Infection (n = 3); myelodysplastic syndrome (n = 3); pulmonary toxicity (n = 2); cardiotoxicity (n = 1); cytokine release syndrome (n = 1); and microangiopathy (n = 1)
[‡]Gastrointestinal malignancy (n = 4); infection (n = 2); stroke/status epilepticus (n = 2); aortic aneurysm (n = 1); gastrointestinal bleeding (n = 1); suicide (n = 1); sudden cardiac arrest (n = 1); and general debility (n = 1)

Supplementary Table 6. Multivariate analyses adjusted for age at ASCT and sex

Characteristics	HR for PFS (95% CI)	*P* value	HR for OS (95% CI)	*P* value
Relapse between 6 to 12 months of frontline therapy completion (vs refractory/relapse <6 months)	0.83 (0.59–1.18)	0.31	0.67 (0.46–0.98)	0.04
1 line of ST (vs >1)	0.53 (0.36–0.77)	0.0008	0.51 (0.35–0.74)	0.0005
CR to ST (vs PR)	0.49 (0.35–0.69)	<0.0001	0.46 (0.32–0.66)	<0.0001

Abbreviations: ASCT, autologous stem cell transplant; PFS, progression-free survival; OS, overall survival: HR, hazard ratio; CI, confidence interval; ST, salvage chemotherapy; CR, complete response; PR, partial response