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Salvage high-dose chemotherapy and autologous stem cell transplant consolidation following relapse after CAR-T cell for large B-cell lymphoma

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Running title: Salvage HDC/ASCT after post CAR-T relapse in LBCL

Key points:

1. Patients who relapse after CAR-T can achieve durable CR after effective high-dose chemotherapy and autologous stem-cell transplant
2. Adequate autologous stem cell doses can still be collected after CAR-T therapy resulting in stable engraftment

1,354/ 1,500 words

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Authorship Contributions

JR and EA equally composed the manuscript and reviewed patient charts.
SA composed manuscript.
MH, AA, FM, and IK pulled patient data.
PS, DC, QB, CH, CP, SN, EJS, and YN referred and managed patients clinically.

Conflict of Interest Disclosures

PS is a consultant for Roche-Genentech, Abbvie-Genmab, Beigene, Ipsen, Kite/Gilead, AstraZeneca-Acerta, ADC Therapeutics, Sobi, and Incyte; he has received research funds from Sobi, AstraZeneca-Acerta, ALX Oncology, Kite Gilead and ADC Therapeutics.

All other Authors list no COI at this time

Data Availability:

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Letter to the Editor:

CD19-directed chimeric antigen receptor T-cell (CAR-T) therapies were first approved for adult patients with relapsed or refractory large B cell lymphoma (LBCL) after 2 or more lines of therapy [1-4] and subsequently trials comparing high-dose chemotherapy with consolidative autologous stem cell transplant (HDC/ASCT) to CAR-T cell therapy in the 2nd line setting for refractory or early relapsing patients demonstrated improved outcomes with CAR-T cell therapy over HDC/ASCT with superior event free survival and overall survival (OS) [5-8]. CAR T-cell therapy is the standard of care for patients with primary refractory/relapsed LBCL.
Outcomes for patients with LBCL who progress after CAR-T per recent reports quote an estimated 12-month OS between 14% and up to 30%, Jain et. al. Given that most patients receiving CAR-T had chemorefractory tumors, the role of HDC/ASCT for CAR-T failure is largely unknown.
We herein describe our experience in patients with LBCL failing CAR-T cell therapy who received salvage therapy followed by consolidation with HDC/ASCT.

Patients ≥18 years old with R/R LBCL who relapse following CD19.CAR-T therapy or were refractory to CAR-T administered for any line of therapy between 2016 - 2024, and consequently received salvage therapy including HDC/ASCT were included in this single center retrospective analysis. All patients referred to the transplant department in the setting of relapse after CAR-T were screened and patients with central nervous system (CNS) lymphoma were included. Data was collected from an institutional database as well as the electronic medical record. Institutional Review Board approval for this retrospective analysis was obtained. Statistical analysis was performed using R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria). Survival outcomes were analyzed using the Kaplan-Meier method for overall survival.

Fifty-six patients were referred to the stem cell transplant department. Thirty five were referred for consideration of Allogeneic transplant, of whom a few were deemed eligible. Twenty one patients were referrals for HDC/ASCT. Of those 21 patients, 6 did not proceed to HDC/ASCT due to the following; 4 patients passed during salvage therapy due to disease progression (PD), 1 patient developed therapy-related myeloid malignancy, 1 patient achieved a complete response (CR) and opted to not pursue HDC/ASCT.

Therefore of our cohort of 21 patients, 15 patients received HDC/ASCT as consolidation post salvage treatment after CAR-T failure**.** The median age was 50 (24-78). The median time to progression after CAR-T, with the start date noted as the day of CAR-T infusion, was 122 days (29 – 501)**.** Two patients had disease refractory to CAR-T and 13 experienced relapse after an initial response to CAR-T. The average time from relapse/progression after CAR-T to HDC/ASCT was 302 days (190-612). A median of 1 (1-2) salvage lines of therapy after CAR-T was given prior to HDC/ASCT **(Table 1).** Only 2 patients were treated with CAR-T in the second line. Immediately prior to HDC/ASCT disease response status was as follows; 8 patients in CR, 6 partial response (PR), and 1 PD.

All patients underwent chemo-mobilization prior to apheresis and had adequate stem cell collection with the exception of one patient who required a second mobilization attempt to achieve the institutional minimum of 3 million CD34+ cells/Kg. All patients receive granulocyte colony-stimulating factor (GCSF) +/- a CXCR4 antagonist.
The average total nucleated cell dose infused x10^8/kg was 15.16 and CD34+ cell dose infused x10^6/kg was 4.05**.** The median times to neutrophil and platelet engraftment were 11 days (9-14) and 21 days (6-112), respectively **[Supplement Table 1].**

The HDC regimen breakdown can be found in Table 1**.** Median follow-up from day 0 of ASCT is 16.5 months/ 496 days (8-1901). Fourteen patients were evaluable at 30 days post ASCT and were in CR. Eleven patients are in CR at 3 years. The 1-year progression-free survival (PFS), overall survival (OS), and non-relapse mortality (NRM) were 67%, 73%, and 6.7% respectively [Fig 1&2]. 3 patients relapsed and died after HDC/ASCT and of these, 2 were from disease progression and 1 was from splenic infarct with hemorrhage**.** One patient passed of early septic shock post HDC prior to engraftment. Of the 3 who relapsed, 1 had CNS involvement and 1 had testicular involvement, known sanctuary sites, as well as their previous chemo-exposure is different and so is the biology of their responses to high dose chemotherapy**.** No secondary malignancies were observed.

Within 100 days of ASCT four patients had bacterial only infections, three patients had viral only infection (one of those was from COVID-19), two had bacterial and viral infection concomitantly, one patient had concomitant bacterial, viral, fungal infections, and finally one had concomitant bacterial, viral, parasitic, fungal infections.

The major challenges posed by CAR-T therapy failures were illustrated in a large analysis of 550 patients from the French CAR-T registry. Failure after CAR-T therapy occurred at a median of 2.7 months. After treatment failure, 64% of patients received salvage treatment with low (14%) response rates and the CR rate was 7%. The median PFS and OS were 2.8 months, and 5.2 months. This multicenter French analysis highlights urgent need for novel treatment strategies for this population. Among the current salvage treatment options, the most recent therapies include bispecific antibodies or antibody drug conjugates. While the response rates of bispecific antibodies and antibody drug conjugates are encouraging, the durability of response has yet to be determined [13]. For a selected patient population allo-HCT has curative potential in the post–CAR-T setting. A retrospective multicenter study in the US identified 88 patients who received an allo-HCT after failure of CAR-T, 76% of whom had responded to the immediately prior salvage therapy. The 1-year PFS, OS, and NRM rates were 45%, 59%, and 22% [9]. Similar results were shown in a retrospective analysis of 39 patients with the 2-year PFS and NRM rates were 31% and 26% [10]. In data published by Ghobadi et al in 2024, of 8 patients who received 3L cellular/immunotherapy, 6 received subsequent SCT (5 Allo and 1 Auto); all 6 were alive at their data cutoff. However, despite its curative potential (particularly for patients in CR at transplant), allo-HCT is limited by its inherently high morbidity and mortality rates and by donor availability and patient suitability.

Our data highlight that in selected patients HDC/ASCT is an effective approach for consolidation as there is no standard consolidation currently for patients who have CAR-T failure in terms of next line of therapy. Mobilization of stem cells post CAR-T was not a barrier and 15 of 16 patients were able to successfully mobilize atleast 3 million cells. The stem cells provided sufficient hematological reconstitution and no patients experienced graft failure. The majority of patients received HDC/ASCT with an intensive conditioning regimen backbone either on clinical trial or per departmental standard. Prior studies have demonstrated efficacy for refractory lymphoma with these regimens [11-12]. The benefit from the addition of Olaparib to the conditioning chemotherapy has recently been described by Nieto et al. showing synergistic cytotoxicity of the four-drug combination which is attributed to activation of the DNA-damage response, inhibition of PARP activity and DNA repair, decreased mitochondrial membrane potential, and increased production of reactive oxygen species, all of which may enhance apoptosis.

We acknowledge the limitations of this data set due to being a retrospective review from a single institution with a cohort which is heterogenous. We also acknowledge that patients received a variety of salvage options but were able to demonstrate some form of disease control prior to HDC/ASCT. We also acknowledge the use of conditioning chemotherapy on a clinical trial, however there is no standard of care in this setting and it was preferred to offer patients a trial option. We should also mention that during the time period of our study, bispecifics were not yet FDA approved. However bispecifics after CAR-T failure has also not yet shown to be curative and does improve OS because OS in this population is dismal in genereal. This therefore indicates our herein presented patient cohort highlights a bias towards responders because non-responders and those who died from progression never received HDC/ASCT.

There is a paucity of data on the optimal treatment for relapsed LBCL after CAR-T cell therapy without clear superiority of any modality. Further studies are needed to better define the profile of patients who will benefit from this approach. Our experience is the largest to date demonstrating efficacy of HDC/ASCT consolidation as an option to provide durable remissions in a subset of patients with an acceptable safety profile.

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Table 1

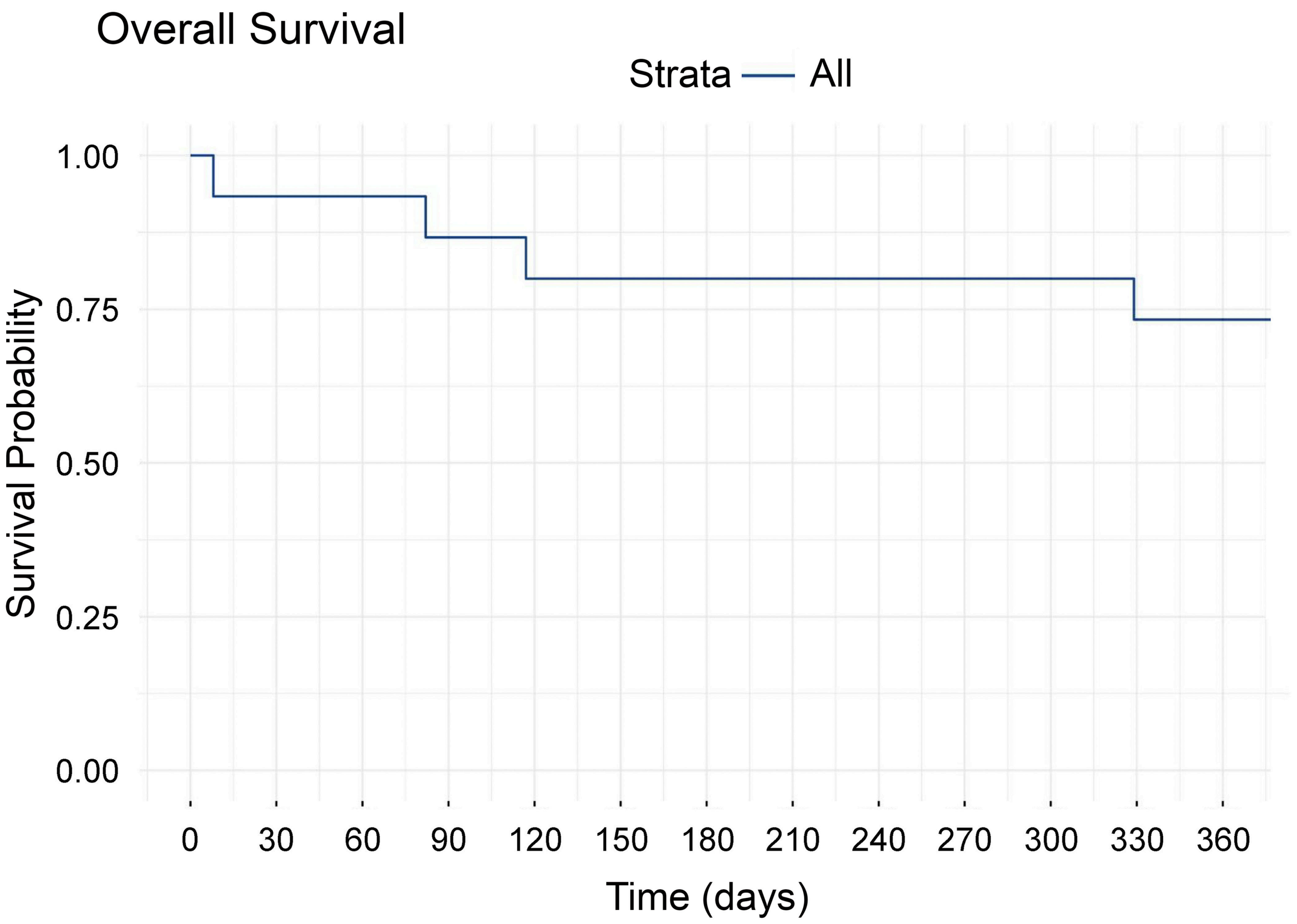
Age	Sex	Diagnosis	No. prior lines	Treatment history and response to each line prior to CAR-T cell therapy	Best response to CAR-T	Duration of response to CAR-T (days)	No. lines post CAR-T, prior ASCT	Treatment received post CAR-T, prior to ASCT	Disease status at ASCT	HDC regimen	Final response to ASCT	Status at time of analysis
64	M	DLBCL	6	Rituximab (NE), Rituximab (CR), Rituximab (PR), Rituximab (PD), CHOP (CR), Polatuzumab (CR)	Refractory	203	1	Rituximab + DeAngelis Regimen (CR)	CR	Thiotepa/Busulfan/Cy	CR	Passed
48	F	DLBCL	5	Rituximab (CR), CHOP (CR), R-Gemcitabine/Oxaliplatin (PD), radiation (SD), HDMTX 3g/m2 (SD)	Relapse	191	1	Ritux + Polatuz + Bendamustine + IT-MTX (CR)	CR	Gemcitabine/Busulfan/Melphalan/Vorinostat/Palifermin/Rituximab/Olaparib	CR	CR
28	F	DLBCL	4	R-EPOCH (PR), R-ICE (PD), Pembrolizumab (PD), Obinutuzumab + DHAP (PR)	Relapse	520	2	Rituximab + Hyper-Cytoxan (PR), R-IE (PR)	PR	Gemcitabine/Busulfan/Melphalan/Vorinostat/Palifermin/Rituximab/Olaparib	CR	Passed
28	F	DLBCL	1	R-EPOCH (SD)	Refractory	28	1	Pembrolizumab (PR)	PR	Gemcitabine/Busulfan/Melphalan/Vorinostat/Rituximab	CR	CR
52	M	DLBCL	2	R-EPOCH (PD), Radiation (NE)	Relapse	20	2	Rituximab (CR), Revlimid (CR)	CR	Gemcitabine/Busulfan/Melphalan/Vorinostat/Revlimid/Rituximab/Palifermin	CR	Passed
69	M	DLBCL	1	R-CHOP + IT MTX (PD)	Relapse	153	1	Rituximab + HD-MTX (CR)	CR	Carmustine/Thiotepa/Rituximab	CR	CR
52	F	DLBCL	2	R-CHOP (PD), Radiation (PD)	Relapse	109	1	Rituximab + Polatuz (CR)	CR	Gemcitabine/Busulfan/Melphalan/Vorinostat/Palifermin/Rituximab/Olaparib	CR	CR
31	M	DLBCL	3	R-CHOP (PD), R-DHAP (SD), Cy/Flu + CAR-NK (PR)	Relapse	102	1	Acalabrutinib + AZD4573 (SD)	SD	Gemcitabine/Busulfan/Melphalan/Vorinostat/Palifermin/Rituximab/Olaparib	CR	CR
48	M	DLBCL	3	R-CHOP (CR), R-IT-MTX (PD),Tafasitamab/Lenalidomide 20mg/d (SD)	Relapse	91	1	Tafasitamab + Lenalidomide 20mg/d (PR)	PR	Gemcitabine/Busulfan/Melphalan/Vorinostat/Palifermin/Rituximab/Olaparib	CR	CR
76	F	DLBCL	5	R-CHOP (CR), R-Bendamustine (NE), Dex, Gemcitabine, Cisplatin (PR), Loncastuximab (PD), Dex + Ritux + HyperCytoxan (CR)	Relapse	91	2	Radiation (PD), Dexamethasone + Ritux + HyperCytox (CR)	CR	BEAM	CR	CR
53	M	DLBCL	2	R-CHOP (PD), R-ICE (PD)	Relapse	91	2	FT516 + IL2 (PD), AZD4573 + Acalabrutinib(CR)	CR	Gemcitabine/Busulfan/Melphalan/Vorinostat/Palifermin/Rituximab/Olaparib	ED	Passed
46	M	DLBCL*	2	AVD + Brentuximab (PD), R-Gemcitabine/Oxaliplatin (PD)	Refractory	111	2	CD19 CAR NK (CR), CD19 CAR NK (CR)	CR	Gemcitabine/Busulfan/Melphalan/Vorinostat/Palifermin/Rituximab/Olaparib	CR	CR
41	F	DLBCL	2	R-CHOP (PD), R-ICE (PR)	Relapse	90	1	Pembrolizumab (PR)	PR	Gemcitabine/Busulfan/Melphalan/Vorinostat/Palifermin/Rituximab/Olaparib	CR	CR
53	M	DLBCL	3	R-CHOP + IT MTX (NE), R- DA-EPOCH + IT MTX (CR), Ibrutinib + Revlimid (PD)	Relapse	90	1	Rituximab + CC-95251 (PR)	PD	Gemcitabine/Busulfan/Melphalan/Vorinostat/Palifermin/Rituximab/Olaparib	CR	
22	M	DLBCL	2	R-ICE (PR), R-Polatuzumab + Bendamustine (PD)	Refractory	29	1	Pembro-GVD (PR)	PR	Gemcitabine/Busulfan/Melphalan/Vorinostat/Palifermin/Rituximab/Olaparib	CR	

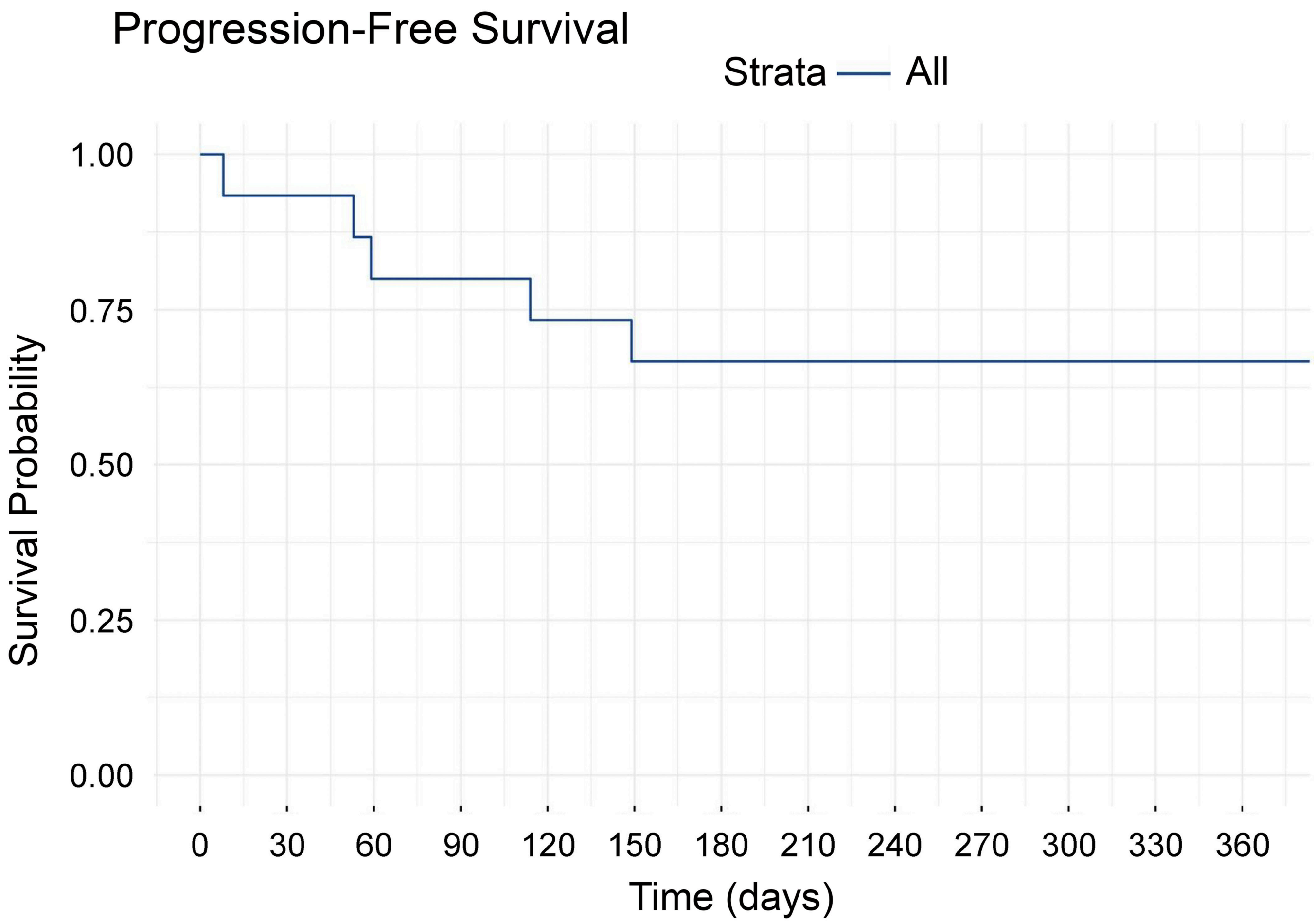
Legend: *ED indicates Early Death*

**Had misdiagnosis from outside center of Hodgkin*

Figure 1. Survival curves

1-year progression-free survival (PFS), overall survival (OS): 67%, 73%, respectively


Overall Survival
Strata — All
Survival Probability
1.00
0.75
0.50
0.25
0.00
0
30
60
90
120
150
180
210
240
270
300
330
360
Time (days)


Progression-Free Survival
Strata — All
Survival Probability
1.00
0.75
0.50
0.25
0.00
0
30
60
90
120
150
180
210
240
270
300
330
360
Time (days)

Supplement

Supplement Table 1

Charactertics of patients who have passed away (4 pts total)	N (%)
# of days between day 0 HCT to death (range)	134 (8-329)
Cause of death	
PD	2 (50%)
Infection (septic shock)	1 (25%)
Hemorrhage (splenic infarct)	1 (25%)

Infections during autoSCT during first 100 days	N (%)
Bacterial	8 (73%)
Viral	7 (63%)
Fungal/Parasitic	2 (18%)

Multiple patients had multiple infection types ongoing during first 100 days

Cell dose and engraftment	Average (range)
TNC dose infused x 10e8/kg	15.16 (5.26-27.309
CD34 dose infused x 10e6/kg	4.05 (1.85-7.75)
Days to WBC 200 from SCT, out of 14 pts	9 (7-10)
Days to ANC 500 from SCT, out of 14 pts	10 (8-13)
Days to ANC 1000 from SCT, out of 14 pts	11 (9-14)
Days to PLT 20K recovery from PLT transfusion, out of 12 pts	9 (0-69)
Days to PLT 50K recovery from PLT transfusion, out of 8 pts	21 (6-112)

CAR-T toxicities (N=14)	N (%)
ICANS	
None/0	10 (71%)
Grade 1	0 (0%)
Grade 2	2 (14%)
Grade 3	2 (14%)
Grade 4	0 (0%)
CRS	
None/0	4 (29%)
Grade 1	5 (36%)
Grade 2	4 (29%)
Grade 3	0 (0%)
Grade 4	1 (7%)

1 patient with unknown data due to CAR-T performed outside MD Anderson. Detailed hospital records are not available