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

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] Subsequent trials comparing high-dose chemotherapy with consolidative autologous stem cell transplant (HDC/ASCT) to CAR-T cell therapy in the second-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. According to recent reports, outcomes for patients with LBCL who progress after CAR-T are an estimated 12-month OS of 14-30%.[9] Given that most patients receiving CAR-T had chemorefractory tumors, the role of HDC/ASCT for CAR-T failure is largely unknown. Here we describe our experience in patients with LBCL failing CAR-T cell therapy who received salvage therapy followed by consolidation with HDC/ASCT.

This single center retrospective analysis included patients ≥18 years old with relapsed/refractory (R/R) LBCL who relapsed 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. 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 were collected from an institutional database as well as from electronic medical records. 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 OS.

Fifty-six patients were referred to the Stem Cell Transplant Department. Thirty-five were referred for consideration of ASCT, 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 for the following reasons: 4 patients passed away during salvage therapy due to disease progression (PD), one patient developed a therapy-related myeloid malignancy, one 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 years (range: 24-78 years). The median time to progression after CAR-T was 122 days (range: 29-501); the start date was noted as the day of CAR-T infusion. 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 (range: 190-612). A median of one (range: 1-2) salvage line 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 one 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 received granulocyte colony-stimulating factor (GCSF) either with or without a CXCR4 antagonist. The average total nucleated cell dose infused $x10^8$/kg was 15.16 and the $CD34^+$ cell dose infused $x10^6$/kg was 4.05. The median times to neutrophil and platelet engraftment were 11 days (range: 9-14) and 21 days (range: 6-112), respectively (*Online Supplementary Table S1*).

A breakdown of the HDC regimen can be found in Table 1. Median follow-up from day 0 of ASCT is 16.5 months (496 days) (range: 8-1,901). Fourteen patients were evaluable at 30 days post ASCT and were in CR. Eleven patients are in CR at three years. The 1-year progression-free survival (PFS), OS, and non-relapse mortality (NRM) were 67%, 73%, and 6.7%, respectively (Figure 1). Three patients relapsed and died after HDC/ASCT; of these, 2 were from disease progression and one was from splenic infarct with hemorrhage. One patient passed away due to early septic shock post HDC prior to engraftment. Of the 3 who relapsed, one had CNS involvement and one had testicular involvement, both being known sanctuary sites. In addition, all 3 of these patients had had different previous chemo-exposure and experienced different biologic responses to high-dose chemotherapy. No secondary malignancies were observed. Within 100 days of ASCT, 4 patients had bacterial only infections, 3 patients had viral only infection (one of those was from COVID-19), 2 had bacterial and viral infection concomitantly, one patient had concomitant bacterial, viral and fungal infections, and, finally, one had concomitant bacterial, viral, parasitic and 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, which showed that failure after CAR-T therapy occurred at a median of 2.7 months.[10]

Table 1. Breakdown of the high-dose chemotherapy regimen.

Age, years	Sex	Diagnosis	N 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	N lines post CAR-T, prior to 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	Died
48	F	DLBCL	5	Rituximab (CR), CHOP (CR), R- Gemcitabine/ Oxaliplatin (PD), radiation (SD), HDMTX 3 g/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	Died
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	Gemictabine/ Busulfan/ Melphalan/ Vorinostat/ Revlimid/ Rituximab/ Palifermin	CR	Died
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

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Age, years	Sex	Diagnosis	N 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	N lines post CAR-T, prior to ASCT	Treatment received post CAR-T, prior to ASCT	Disease status at ASCT	HDC regimen	Final response to ASCT	Status at time of analysis
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 20 mg/d (SD)	Relapse	91	1	Tafasitamab + Lenalidomide 20 mg/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	Died
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

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Age, years	Sex	Diagnosis	N 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	N lines post CAR-T, prior to ASCT	Treatment received post CAR-T, prior to ASCT	Disease status at ASCT	HDC regimen	Final response to ASCT	Status at time of analysis
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	

ASCT: autologous stem cell transplantation; AVD: doxorubicin, vinblastine, dacarbazine; CAR-T: chimeric antigen receptor T-cell therapy; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisolone; CR: complete response; Cy: cyclophosphamide; DHAP: dexamethasone, high-dose cytarabine, cysplatin; DLBCL: diffuse large B-cell lymphoma; ED: early death; F: female; Flu: fludarabine; HDC: high-dose chemotherapy; HDMTX: high-dose methotrexate IT-MTX: intrathecal MTX; HyperCytoxan: hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone; M: male; N: number; NE: not evaluable; PD: progressive disease; Pembro-GVD: pembrolizumab-gemcitabine, vinorelbine, liposomal doxorubicin; PR: partial response; R: rituximab; R-EPOCH: rituximab-etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; R-DA- EPOCH: rituximab + dose-adjusted EPOCH; R-ICE: rituximab-ifosfamide, carboplatin, etoposide; R-IE: rituximab-ifosfamide, etoposide; SD: stable disease. *Patient had been misdiagnosed with Hodgkin lymphoma at another center.

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, respectively. This multicenter French analysis highlights the 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.[11] For a selected patient population, allogeneic (allo)HCT has curative potential in the post-CAR-T setting. A retrospective multicenter study in the US identified 88 patients who received an alloHCT after failure of CAR-T, 76% of whom had responded to the immediately administered salvage therapy prior to transplant. The 1-year PFS, OS, and NRM rates were 45%, 59%, and 22%, respectively.[12] Similar results were shown in a retrospective analysis of 39 patients with the 2-year PFS and NRM rates were 31% and 26%, respectively.[13] 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 autologous); all 6 were alive at their data cutoff. However, despite its curative potential (particularly for patients in CR at transplant), alloHCT is limited by its inherently high morbidity and mortality rates and compromised by donor availability and patient suitability.

Our data highlight that, in selected patients, HDC/ASCT is an effective approach for consolidation; this is important as currently there is no standard consolidation 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 at least 3 million cells. The stem cells provided sufficient hematologic 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.[14,15] The benefit from the addition of

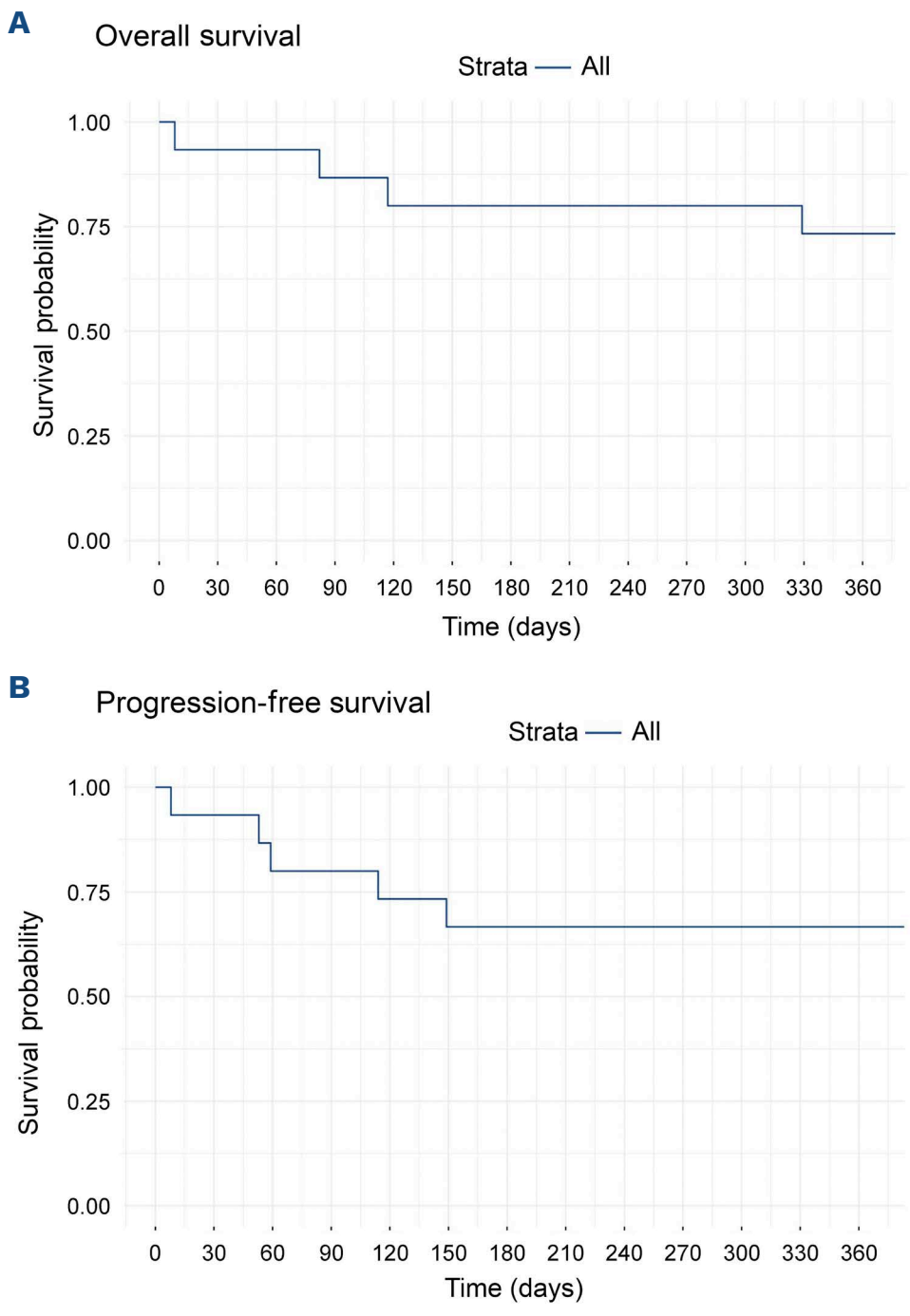


Figure 1. Survival curves. (A) One-year overall survival (73%) and (B) one-year progression-free survival (67%).

Olaparib to the conditioning chemotherapy has recently been described by Nieto *et al*.[15] They showed synergistic cytotoxicity of the 4-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 imposed by the retrospective nature of the review from a single institution with a heterogenous cohort. 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 considered preferable to offer patients a trial option. We should also mention that during the time period of our study, bispecifics had not yet received Food and Drug Administration approval. The use of bispecifics after CAR-T failure had also not yet been shown to be curative; these improve OS rates, which in this population are generally dismal. This, therefore, indicates that our patient cohort here highlights a bias towards responders, as 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.

Authors

Jeremy Ramdial,[1] Erica Agbadiba,[2] Misha Hawkins,[2] Amy Ayers,[2] Farzaneh Maadani,[1] Indreshpal Kaur,[1] Paolo Strati,[2] Dai Chihara,[2] Qaiser Bashir,[1] Chitra Hosing,[1] Chelsea Pinnix,[3] Sattva Neelapu,[2] Elizabeth J. Shpall,[1] Yago Nieto[1] and Sairah Ahmed[2]

[1]Department of Stem Cell Transplant and Cellular Therapy; [2]Department of Lymphoma and Myeloma and [3]Department of Radiation-Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Correspondence:
J. RAMDIAL - jlramdial@mdanderson.org

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Contributions

JR and EA both prepared the manuscript and reviewed patient charts; SA wrote the manuscript; MH, AA, FM and IK collected patient data; PS, DC, QB, CH, CP, SN, EJS and YN referred patients and are responsible for their clinical management.

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Data-sharing statement

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

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