Salvage radiotherapy in relapsed/refractory large B-cell lymphoma after failure of CAR T-cell therapy

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Abstract

Despite the success of CD19-targeted chimeric antigen receptor (CAR T)-cell therapy in patients with relapsed/refractory large B-cell lymphoma (LBCL), there is a need for effective salvage strategies post-CAR T-cell therapy failure. We conducted a multi-institutional retrospective study of patients who relapsed following CAR T-cell therapy (axicabtagene ciloleucel [axi-cel] or tisagenlecleucel [tisa-cel]) and received salvage therapies (radiation therapy [RT] alone, systemic therapy alone, or combined modality therapy [CMT]). A total of 120 patients with post-CAR T relapsed LBCL received salvage therapies (RT alone, 25 patients; CMT, 15 patients; systemic therapy alone, 80 patients). The median follow-up from CAR T-cell infusion was 10.2 months (interquartile range, 5.2-20.9 months). Failure occurred in previously involved sites prior to CAR T-cell therapy in 78% of patients (n=93). A total of 93 sites were irradiated in 54 patients who received any salvage RT post-CAR T failure. The median dose/fractionation were 30 Gy (range, 4-50.4 Gy) and 10 fractions (range, 1-28 fractions). The 1-year local control rate for the 81 assessable sites was 84%. On univariate analysis, the median overall survival (OS) from the start date of RT was significantly higher among patients who received comprehensive RT *versus* focal RT (19.1 months *vs*. 3.0 months; *P*=<0.001). Twenty-three of 29 patients who received comprehensive RT had limited-stage disease. Among these, there was no difference in median OS among the patients who received RT alone *versus* those who received RT followed by additional therapies (log-rank *P*=0.2). On multivariate survival analysis, achieving PR or CR post-CAR T (hazard ratio =0.5; 95% confidence interval: 0.3-0.9; *P*=0.01) was independently associated with superior OS. Our findings suggest that RT can provide local control for LBCL relapsed post-CAR T-cell therapy, particularly in patients with limited-stage relapsed disease treated with comprehensive RT.

Introduction

CD19-targeted chimeric antigen receptor (CAR T)-cell therapy has transformed the treatment of relapsed/refractory large B-cell lymphoma (rel/ref LBCL). The landmark CAR T-cell therapy trials in rel/ref LBCL have shown durable remissions in approximately 40%[1–3] of patients who would otherwise have poor prognoses using conventional therapies. Despite these favorable outcomes, more than half of all patients undergoing CAR T-cell therapy will develop progressive disease, leaving these patients in need of additional therapies post-CAR T failure.

Potential biologic rationales have been purported for CAR T-cell therapy failure, related to CAR T cells, lymphoma, or microenvironment. These include downregulation of the tumor-associated antigen or loss of the target antigen,[4–6] T-cell exhaustion, or senescence,[7–9] intrinsic CAR T-cell dysfunction, inadequate persistence or expansion of the CAR T cells *in vivo*,[10,11] inadequate memory phenotype achieved by the CAR T cells[3,12,13] and/or microenvironment-induced immune suppression.[14–16]

The optimal approach following failure of CAR T-cell therapy is unknown. Potential therapeutic options include systemic therapy including a targeted agent (such as polatuzumab vedotin, tafasitimab/lenalidomide, or loncastuximab tesirine), radiation therapy (RT), allogeneic hematopoietic stem cell transplantation (HSCT), second CAR T-cell therapy infusion, or any combinatorial treatment based on these modalities. Bispecific mono-

clonal antibodies, such as epcoritamab-bysp, which recently received accelerated approval by the Food and Drug Administration (FDA), are also inducing responses in the post-CAR T-cell setting. An important goal for treatment post-CAR T-cell therapy is to modulate the immune system and exert synergistic activity with CAR T cells, thus overcoming resistance and leading to durable remissions.[17–24]

Of late, there is a burgeoning interest in exploring RT after CAR T-cell failure due to immunomodulatory and potentially synergistic effects that may interplay between radiation therapy and cellular immunotherapies. In addition to the role of RT as a local therapy, it is even more compelling that RT has the potential to prime and act in concert with CAR T cells to achieve long-lasting remissions.[16,25] Preclinical mechanistic studies have previously highlighted the synergy between RT and CAR T-cell therapy using cell lines of solid tumors.[26,27] It was shown that low-dose RT might radiosensitize tumor cells by upregulating specific cytokines, leading to the trafficking of modified T cells into the irradiated sites. Furthermore, it was revealed that RT could lead to enhanced T-cell receptor (TCR) repertoire expansion by inducing an abscopal-like effect outside the radiation field, as was described in a case of multiple myeloma.[28]

Data available pertaining to the optimal salvage strategy following CAR T-cell therapy failure is limited to a few case series published to date.[17–19,22–24] In an effort to unravel the ambiguity concerning the therapeutic dilemmas in patients progressing after CAR T-cell therapy, we sought to describe our multi-institutional experience to compare the impact of RT with other systemic regimens in LBCL patients who progressed following CD19-targeted CAR T-cell therapy.

Methods

Following Institutional Review Board approval, a multi-institutional retrospective study was conducted at two tertiary care centers for consecutive LBCL patients who received either tisagenlecleucel (tisa-cel) or axicabtagene ciloleucel (axi-cel) CAR T-cell therapy between 2017 and 2021 as part of a database of 352 patients. Eligible patients had rel/ref LBCL including the following: *de novo* diffuse large-B cell lymphoma (DLBCL); transformed follicular lymphoma (TFL); DLBCL arising from other low-grade lymphomas; primary mediastinal large B-cell lymphoma (PMBCL); high-grade BCL not otherwise specified/ with rearrangement of MYC with BCL2, or BCL6, or both; B-cell lymphoma unclassifiable with features intermediate between DLBCL and classic Hodgkin lymphoma; or high-grade BCL with features intermediate between DLBCL and Burkitt's lymphoma. In cases of transformed low-grade lymphomas, demographics and patient characteristics were collected from the date of transformation.

Eligible patients had experienced CAR T-cell failure, defined as refractory disease or relapse after initial response following CAR T-cell therapy, and received additional lymphoma-directed therapies. These patients were identified and analyzed using descriptive and statistical analysis. Salvage regimens were categorized into three groups: (i) RT delivered as a single treatment; (ii) systemic therapy, including as chemotherapy, checkpoint inhibitors, other targeted therapies, second CAR T infusion, and allogeneic HSCT; and (iii) combined-modality therapy (CMT), which included only patients who had been planned for both RT and systemic therapy as a first salvage regimen, regardless of the response to either. All three categories were defined at the time of the first salvage therapy following CAR T-cell therapy failure.

The median follow-up was analyzed at two separate time points: the date of CAR T-cell therapy infusion and the start date of salvage therapy post-CAR T failure. Overall survival (OS1) was defined as the time between the date of CAR T-cell therapy infusion and the time of the last follow-up or death from any cause. OS2 was defined as the time from the start date of salvage therapy until the time of the last follow-up or death from any cause. To account for the heterogeneity of the cohort and consider all possible combinations of patients, subgroup analyses were also performed in the OS2 analysis. These analyses focused on two groups: patients who initially received systemic therapy and subsequently had disease progression for which they required RT and patients who received comprehensive RT and then experienced disease progression for which they received systemic therapy. Event-free survival (EFS1) was defined as the time from CAR T-cell therapy infusion until the date of disease progression, relapse, start of a new line of lymphoma therapy, or death from any cause. EFS2 was defined as the time from the start date of the first salvage therapy post-CAR T failure until the date of disease progression, relapse, or start of a new line of lymphoma therapy, or death from any cause, whichever occurs earlier.

Early response was generally assessed at post-CAR T day 30 (interquartile range [IQR], 28-31 days), while the best overall response was assessed at any time between post-CAR T-cell therapy and additional salvage therapies when there was the lowest disease burden. The overall response rate (ORR) was defined as the percentage of patients who achieved complete response (CR) or partial response (PR). In-field response for salvage RT was evaluated using post-RT imaging and/or clinical assessment and then was analyzed based on the total number of irradiated sites. The in-field PFS was defined as the time between the start date of RT and the date of in-field progression/relapse.

A separate analysis was then performed for patients who were treated with comprehensive *versus* focal RT. Com-

prehensive RT in this setting was defined as RT administered to include all lymphoma sites as per the scan obtained immediately prior to the start of RT; patients with relapse in only one site who received RT were considered to have had comprehensive RT. Only the first RT course was included in this analysis for patients receiving >1 salvage RT course. For comparability between different dose/fractionation regimens, the biologically effective dose (BED) was calculated using an α/β ratio of 10. Further information on methodology and details of the statistical analysis are provided in *the Online Supplementary Appendix*.

Results

Patient and treatment characteristics

Online Supplementary Table S1 outlines patient characteristics prior to CAR T-cell therapy infusion. A total of 120 patients meeting eligibility progressed following CAR T-cell therapy and went on to receive salvage therapies: 25 patients received RT alone, 15 patients received CMT, and 80 patients received systemic therapy alone. There was no significant difference in patient characteristics at the time of receiving salvage therapy between the RT, CMT, and systemic therapy cohorts, except for high LDH level (0.006) and Eastern Cooperative Oncology Group (ECOG) performance status (<0.001) (Table 1). The best ORR was 70% (n=84), 43% (n=51) of which were in CR, with a median time to CR being 1.0 month (range, 0.9-5.3 months) post-CAR T infusion. For patients who responded to CAR T, the median duration of response was 3.9 months (IQR, 3.0-6.6 months).

Failure after CAR T-cell infusion

The median time interval between CAR T-cell infusion and treatment failure was 3.0 months (IQR, 1.1-5.1 months) for the entire cohort, with a median follow-up after CAR T-cell infusion of 10.2 months (IQR, 5.2-20.9 months). Analysis of patterns of failure revealed that the majority of patients (n=93, 78%) had a component of failure in previously involved sites pre-CAR T, wherein 35 patients had failed in these sites alone (29%), and 58 patients (48%) had concurrent local and *de novo* failures. The remaining 27 patients (23%) demonstrated *de novo* failures. Of the 67 evaluable patients for CD19 antigen expression status at the time of failure, 59 patients (88%) had CD19-positive disease, and only eight patients (12%) demonstrated CD19-negative disease.

Survival following post-CAR T salvage therapy

The median number of lines of salvage therapy following CAR T-cell failure was 2 (range, 1-8), with a median follow-up after post-CAR T salvage therapy of 5.6 months (IQR, 1.9-12.1 months). The median duration from CAR T-cell infusion to the start date of salvage therapy was 3.4 months (IQR, 1.7-6.5 months). The median OS1 was 15.0 months (95% confidence interval [CI]: 11.7-24.4) and the median OS2 was 9.8 months (95% CI: 6.3-18.6). The estimated 12-month and 24-month OS1 rates were 58% and 39%, respectively. The estimated 12-month and 24-month OS2 rates were 45% and 33%, respectively. The median EFS1 was 3.0 months (95% CI: 2.4-3.2). Kaplan–Meier survival curves of OS1 and EFS1 are illustrated in Figure 1A, B. The median EFS2 was 2.6 months (95% CI: 1.7-4.3). After stratifying by salvage regimen, the median OS2 was not

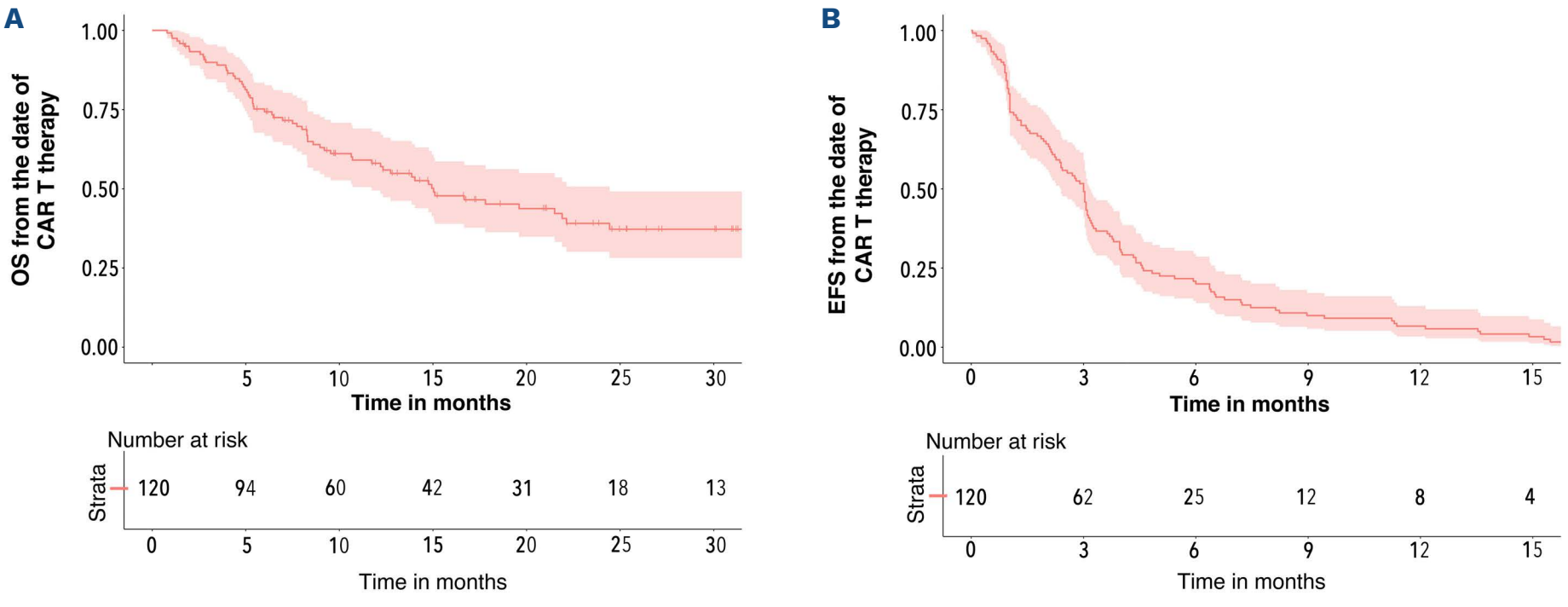

Figure 1. Kaplan–Meier survival estimates of overall survival and event-free survival from the date of CAR T-cell therapy. (A) K-M curve of overall survival (OS1) and (B) K-M curve of event-free survival (EFS1). OS1 was defined as the time between the date of CAR T-cell therapy infusion and the time of the last follow-up or death from any cause. EFS1 was defined as the time from CD19-targeted chimeric antigen receptor (CAR T)-cell therapy infusion until the date of disease progression, relapse, start of a new line of lymphoma therapy, or death from any cause.

reached for the RT group, 7.3 months for the CMT group, 6.6 months for the systemic therapy group, 6.9 months for the systemic therapy then RT group, and 15.6 months for the RT then systemic therapy group. There was no significant difference in OS2 between the five groups based on the type of salvage therapy (*P*=0.6) (Figure 2A). The

Table 1. Characteristics of patients following CAR T-cell therapy infusion.

	RT N (%) (N=25)	CMT N (%) (N=15)	ST N (%) (N=80)	Overall N (%) (N=120)	*P*
Bridging therapy					
Yes	12 (48.0)	8 (53.3)	38 (47.5)	58 (48.3)	0.917
No	13 (52.0)	7 (46.7)	42 (52.5)	62 (51.7)	
CAR T product					
Axi-cel	14 (56.0)	10 (66.7)	58 (72.5)	82 (68.3)	0.298
Tisa-cel	11 (44.0)	5 (33.3)	22 (27.5)	38 (31.7)	
Best response post-CAR T					
CR	12 (48.0)	5 (33.3)	34 (42.5)	51 (42.5)	0.747
PR	8 (32.0)	6 (40.0)	19 (23.8)	33 (27.5)	
DP	5 (20.0)	4 (26.7)	26 (32.5)	35 (29.2)	
SD	0 (0)	0 (0)	1 (1.3)	1 (0.8)	
CNS disease at time of salvage therapy					
Yes	5 (20.0)	2 (13.3)	13 (16.3)	20 (16.7)	0.848
No	20 (80.0)	13 (86.7)	67 (83.8)	100 (83.3)	
Bulky disease at time of salvage therapy*					
≥5 cm	5 (25.0)	5 (38.5)	21 (31.3)	31 (31.0)	0.61
<5 cm	15 (75.0)	7 (53.8)	42 (62.7)	64 (64.0)	
Missing	0 (0)	1 (7.7)	4 (6.0)	5 (5.0)	
Number of disease sites at time of salvage therapy					
≥2	15 (60.0)	10 (66.7)	61 (76.3)	86 (71.7)	0.261
<2	10 (40.0)	5 (33.3)	19 (23.8)	34 (28.3)	
Extranodal disease at time of salvage therapy					
Yes	18 (72.0)	12 (80.0)	61 (76.3)	91 (75.8)	0.839
No	7 (28.0)	3 (20.0)	19 (23.8)	29 (24.2)	
ECOG PS at time of salvage therapy					
0	12 (48.0)	2 (13.3)	15 (18.8)	29 (24.2)	<0.001
1	9 (36.0)	9 (60.0)	53 (66.3)	71 (59.2)	
2	1 (4.0)	4 (26.7)	9 (11.3)	14 (11.7)	
3	0 (0)	0 (0)	3 (3.8)	3 (2.5)	
4	3 (12.0)	0 (0)	0 (0)	3 (2.5)	
Stage at time of salvage therapy					
I	9 (36.0)	4 (26.7)	11 (13.8)	24 (20.0)	0.0872
II	7 (28.0)	2 (13.3)	16 (20.0)	25 (20.8)	
III	1 (4.0)	0 (0)	9 (11.3)	10 (8.3)	
IV	8 (32.0)	9 (60.0)	44 (55.0)	61 (50.8)	
Elevated LDH at time of salvage therapy					
Yes	8 (32.0)	11 (73.3)	52 (65.0)	71 (59.2)	0.00671
No	17 (68.0)	4 (26.7)	28 (35.0)	49 (40.8)	
IPI score at time of salvage therapy					
1	12 (48.0)	2 (13.3)	14 (17.5)	28 (23.3)	0.085
2	5 (20.0)	5 (33.3)	23 (28.8)	33 (27.5)	
3	4 (16.0)	4 (26.7)	24 (30.0)	32 (26.7)	
4	4 (16.0)	4 (26.7)	19 (23.8)	27 (22.5)	
Disease status at time of last follow-up					
CR	6 (24.0)	3 (20.0)	27 (33.8)	36 (30.0)	0.24
PR	2 (8.0)	0 (0)	1 (1.3)	3 (2.5)	
DP	17 (68.0)	12 (80.0)	52 (65.0)	81 (67.5)	
Alive status					
Deceased	12 (48.0)	9 (60.0)	43 (53.8)	64 (53.3)	0.756
Living	13 (52.0)	6 (40.0)	37 (46.3)	56 (46.7)	

χ^2 test was used to compare categorical variables, and ANOVA test was used to compare the means between 3 groups. CAR T: CD19-targeted chimeric antigen receptor; RT: radiation therapy; CMT: combined modality therapy; ST: systemic therapy; CR: complete response; PR: partial response; DP: disease progression; SD: stable disease; CNS: central nervous system; ECOG: Eastern Cooperative Oncology Group; PS: performance status; LDH: lactate dehydrogenase; IPI: International Prognostic Index. Axi-cel: axicabtagene ciloleucel; Tisa-cel: tisagenlecleucel. *Patients with central nervous system lymphoma were excluded.

median EFS2 was 3.5 months for the RT group, 3.3 months for the CMT group, and 1.9 months for the systemic therapy group. There was no significant difference in EFS2 between the three groups based on the type of salvage therapy (*P*=0.84) (Figure 2B).

Salvage radiation therapy following CAR T-cell therapy failure

Fifty-four patients received any salvage RT post-CAR T failure, with a total of 93 sites were irradiated; eight patients (15%) had previously received bridging RT, and among them, one patient received salvage RT to the same site. The median time from CAR T-cell therapy infusion to RT start was 7.7 months (IQR, 3.1-14.4 months). The median dose/fractionation were 30 Gy (range, 4-50.4 Gy) and 10 fractions (range, 1-28 fractions). Irradiated sites were treated via 3-dimensional conformal techniques (3DCRT) (n=51, 64%), intensity-modulated radiation therapy (IMRT) (n=20, 25%), both 3DCRT/IMRT techniques (n=6, 7%), or electron beam (n=3, 4%). Radiation details were incomplete for 13 sites that were administered RT at outside institutions. Sites of RT included: central nervous system (CNS) (n=22, 24%), extremities (n=20, 21.5%), head and neck (n=14,15%), pelvis (n=13, 14%), abdomen (n=10, 11%), chest (n=7, 7.5%), and paraspinal area (n=7, 7.5%). Of the 75 sites assessable per positron emission tomography/computed tomography (PET/CT), 30 sites (40%) were bulky (≥5 cm) at the time of RT. The other 18 sites were not assessable per PET/CT as they were CNS. The in-field responses of the 81 evaluable sites were as follows: CR (n=48, 59%), PR (n=19, 23%), stable disease (n=3, 4%), and in-field progression (n=11, 14%); the remaining 12 sites (13%) were not evaluable since those patients died shortly after receiving RT due to progressive lymphoma. The 1-year LC rate for the 81 assessable sites was 84% (Figure 3). For the 11 sites that experienced recurrence, the median time to in-field progression was 3.4 months (range, 0.6-14.8 months; IQR, 2.3-7.0 months). On univariate analysis, in-field PFS for bulky sites as compared to non-bulky sites was not statistically different (median in-field PFS: 14.8 months *vs*. not reached; log-rank *P*= 0.6); bulky sites were not treated to higher BED_{10} (>30 Gy) as compared to non-bulky sites (*P*=0.7).

Comparative subgroup analysis: comprehensive radiation therapy *versus* focal radiation therapy

A total of 54 patients were treated to 62 sites with a median of one irradiated site (range, 1-2 sites) during their first course of RT and formed the cohort of the comprehensive *versus* focal RT analysis. Twenty-nine patients were treated with comprehensive RT field to 32 sites with a median dose of 36.7 Gy (range, 4-50.4 Gy) while 25 patients were treated with focal RT field to 30 sites with a median dose of 30 Gy (range, 4-41.4 Gy) (*P*< 0.001). Radiation details were incomplete for 12 sites that were administered RT at outside institutions. On univariate

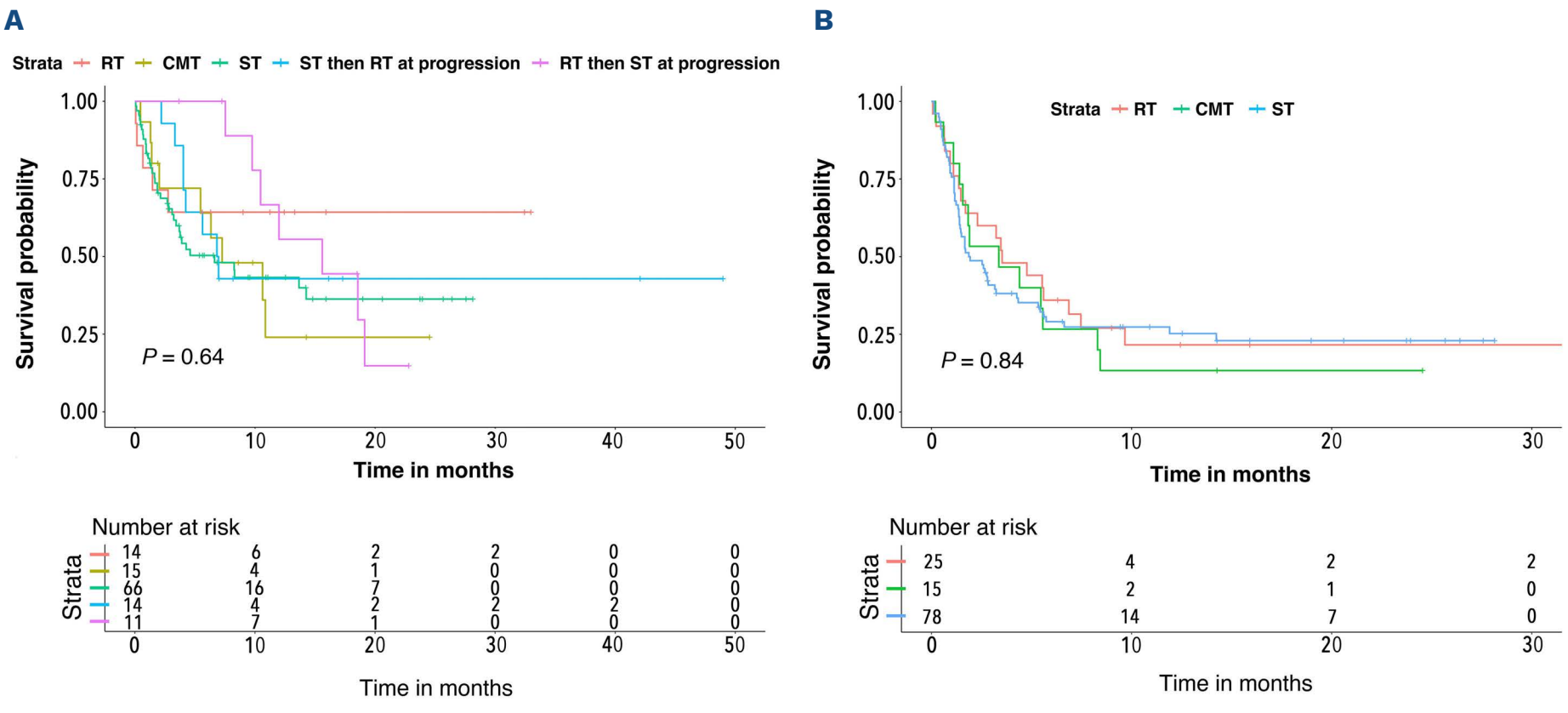

Figure 2. Kaplan–Meier estimates of median overall survival and event-free survival of patients who received salvage therapies following CAR T-cell therapy failure based on the type of salvage therapy. (A) K-M curve of median overall survival (OS2) and (B) K-M curve of median event-free survival (EFS2). OS2 was defined as the time from the start date of salvage therapy until the time of the last follow-up or death from any cause. EFS2 was defined as the time from the start date of the first salvage therapy post- CD19-targeted chimeric antigen receptor (CAR T) failure until the date of disease progression, relapse, or start of a new line of lymphoma therapy, or death from any cause, whichever occurs earlier. RT: radiation therapy; CMT: combined modality therapy; ST: systemic therapy.

analysis, higher OS was observed among patients who received high-dose RT (BED_{10}>30 Gy) as compared to patients who received low-dose RT (BED_{10}≤30 Gy) (median OS: 10.9 months *vs*. 2.0 months; log-rank *P*=0.006); all but one patient treated comprehensively received high-dose RT. There was no statistically significant difference in BED_{10} in sites with local failure vs. sites that remained locally controlled.

Patients who received focal RT were more likely to have an IPI of ≥3 (*P*=<0.001), advanced-stage disease (*P*=<0.001), ≥2 sites of disease (*P*=0.04), extranodal disease (*P*=0.003), and bulky disease as per PET/CT (*P*=0.02). No significant difference was detected among patients with elevated LDH (*P*=0.4) and poor ECOG PS (*P*=0.16). The in-field responses of the 30 evaluable sites for patients who were treated with comprehensive RT were as follows: CR (n=17, 57%), PR (n=7, 23%), and in-field progression (n=6, 20%). The in-field responses of the 24 evaluable sites for patients who were treated with focal RT were as follows: CR (n=12, 50%), PR (n=8, 33%), stable disease (n=3, 13%), and in-field progression (n=1, 4%). The other sites were not assessable since those patients succumbed shortly following RT due to progressive disease. The median survival among patients who received comprehensive RT was 19.1 months and for focal RT was 3.0 months (*P*=<0.001) (Figure 4). In the comprehensive RT group, only three patients received RT to more than one site. On univariate analysis, there was no difference in median OS among the patients who received RT to only one site *versus* those who received RT to two sites (log-rank *P*=0.2). Twenty-three of 29 patients who received comprehensive RT had limited-stage disease, while two patients who received focal RT had limited-stage disease. Among patients who received comprehensive RT with limited-stage disease, there was no difference in median OS among the patients who received RT alone *versus* those who received RT followed by additional therapies (log-rank *P*=0.2).

It is noteworthy that five patients received RT peri-allogeneic HSCT following CAR T-cell failure, including four patients who achieved a CR after RT and systemic therapy, enabling them to proceed with HSCT. The median time from salvage RT to transplant was 5.4 months (range, 3.9-8.9 months). One of the four patients also received additional RT 2 months post-HSCT. The fifth patient received consolidative RT 6 months post-HSCT. At the time of the last follow-up, four patients achieved CR and one patient had disease progression thereafter. All five patients are still alive at a median of 8.8 months (range, 3.3-33.6 months) following allo-HSCT.

Univariate and multivariate analyses

The next step of the analysis focused on factors associated with OS1, OS2, and EFS2 after any therapy following CAR T-cell failure. On univariate analysis, patients who experienced PR or CR post-CAR T-cell therapy infusion had superior OS1 compared to non-responders (median OS1 19.6 months *vs*. 8.3 months; *P*=0.01). Receipt of bridging therapy and type of CAR T product were not associated with OS1. On multivariate analysis, achieving PR or CR post-CAR T (HR=0.5; 95% CI: 0.3-0.9; *P*=0.01) was independently associated with a superior OS1.

Online Supplementary Table S2 outlines the univariate analysis results for OS from the salvage therapy start date (OS2). Factors at the time of receiving salvage therapy that

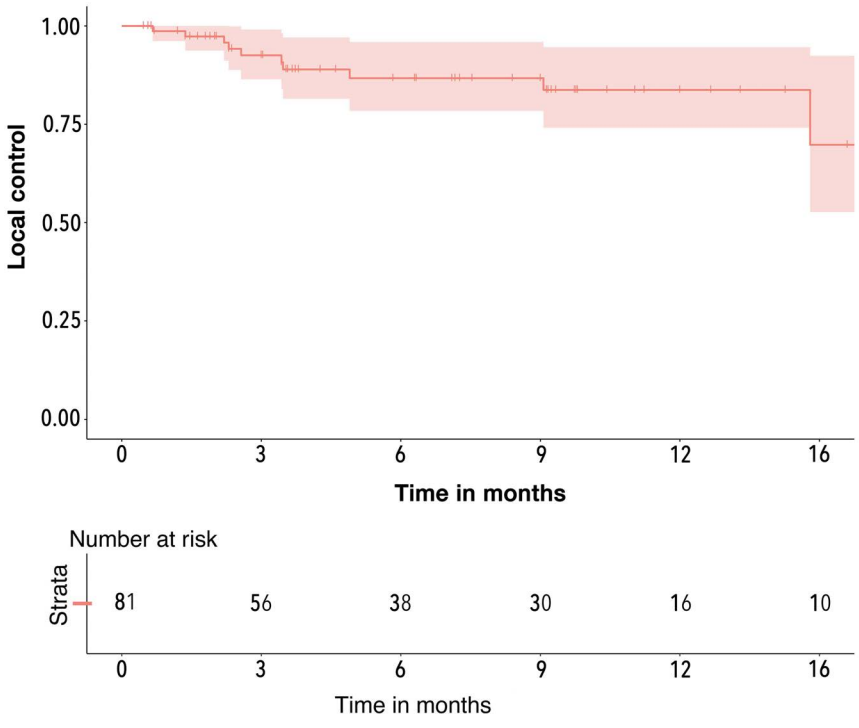

Figure 3. Kaplan–Meier estimate of local control rate for the 81 assessable sites treated with salvage radiation therapy following CAR T-cell therapy failure. CAR T: CD19-targeted chimeric antigen receptor.

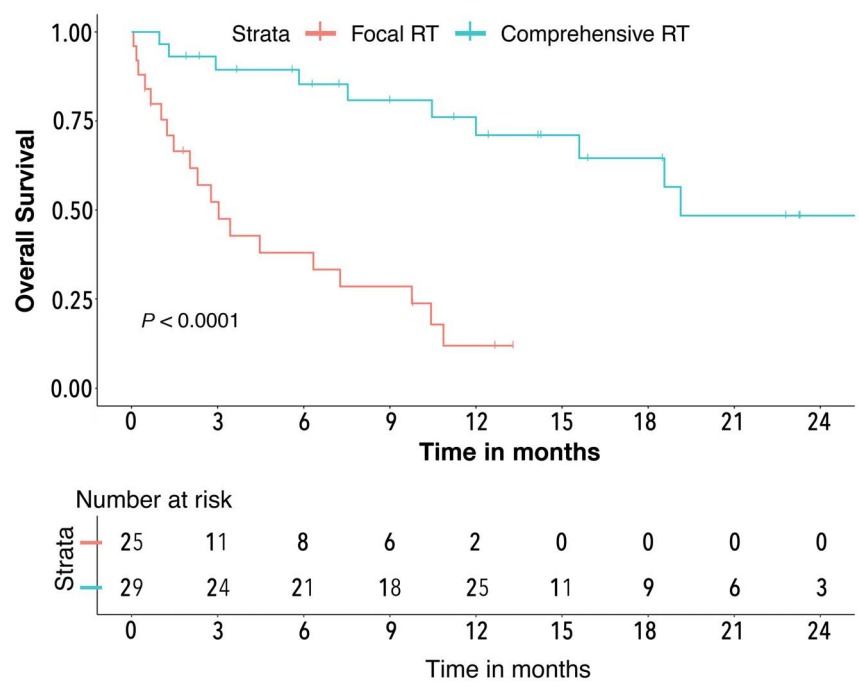

Figure 4. Kaplan-Meier estimate of overall survival of patients who were treated with focal radiation therapy compared to patients treated with comprehensive radiation therapy. Only the first radiation therapy (RT) course was included in this analysis for patients receiving >1 salvage RT course.

predicted for inferior OS2 included presence of bulky disease (≥5 cm) (median OS2 4.0 months *vs*. 12.0 months; *P*=0.03), presence of ≥2 sites of disease (median OS2 6.8 months *vs*. 19.1 months; *P*=0.01), poor performance status (median OS2 2.9 months *vs*. 10.5 months; *P*=0.01), advanced-stage disease (median OS2 4.3 months *vs*. 19.1 months; *P*=0.002), elevated lactate dehydrogenase (LDH) (median OS2 4.0 months *vs*. not reached; *P*=<0.001), and IPI≥3 (median OS2 4.0 months *vs*. 15.6 months; *P*=<0.001). On multivariate analysis, advanced-stage disease (HR=2.2; 95% CI: 1.3-3.8; *P*=0.004) and elevated LDH (HR=2.9; 95% CI: 1.7-5.3; *P*=<0.001) at the time of receiving salvage therapy were independent factors associated with a shorter OS2.

Online Supplementary Table S3 outlines the univariate analysis results for EFS2. Factors at the time of receiving salvage therapy that predicted for inferior EFS2 included presence of ≥2 sites of disease (median EFS2 1.9 months *vs*. 5.5 months; *P*=0.04), extranodal disease (median EFS2 1.8 months *vs*. 5.1 months; *P*=0.04), poor performance status (median EFS2 1.2 months *vs*. 3.2 months; *P*=0.02), advanced-stage disease (median EFS2 1.7 months *vs*. 5.6 months; *P*=<0.001), elevated LDH (median EFS2=1.6 months *vs*. 4.4 months; *P*=0.005), and IPI ≥3 (median EFS2 1.7 months *vs*. 5.4 months; *P*=0.001). On multivariate analysis, advanced-stage disease (HR=2.3; 95% CI: 1.4-3.6; *P*=<0.001) and elevated LDH (HR=1.7; 95% CI: 1.1-2.7; P=0.01) at the time of receiving salvage therapy were independent factors associated with a shorter EFS2.

Discussion

CAR T-cell therapy has redefined the treatment paradigm for heavily pretreated relapsed/refractory LBCL patients. The pivotal CAR T trials, ZUMA-1,[1] JULIET,[2] and TRANSCEND,[3] showed impressive outcomes with response rates ranging from 52% to 82% and 1-year OS rates ranging between 48% and 59%. While these trials led to the approval of CD19-targeted CAR T-cell therapy, questions remain regarding salvage strategies following CAR T-cell failure, which represents the majority of patients. Therefore, investigation of strategies to address CAR T failure is of paramount importance.

To date, only a few studies have reported the real-world experience with using salvage therapies following CAR T-cell failure.[17–19,22–24] To the best of our knowledge, we report the largest study thus far, which has explored the role of RT in comparison with other therapies in depth. We investigated the role of RT in treating local/distant recurrences post-CAR T and compared the impact of RT with other systemic regimens in the salvage setting. Our data showed that patients who received RT alone post-CAR T had superior median OS2 and EFS2 as compared to the other groups, which could be attributed to the favorable baseline risk factors at the time of salvage regimen receipt, particularly the higher likelihood of limited stage disease in patients selected to receive RT alone. Our findings demonstrate that RT can be an important treatment option following CAR T-cell therapy failure, aligning with previous series that support the use of RT for relapse after primary therapy of DLBCL.[29,30]

RT has been established as a fundamental modality in the management of LBCL. It has been shown that RT can improve patient outcomes for aggressive BCL that demonstrate resistance to systemic therapy.[31–33] In the cellular therapy era, RT, in addition to its local control benefits, may enhance the efficacy of CAR T-cell therapy through its broad immunomodulatory roles and immunogenic effects on the immune system.[16,25] Mechanistically, a plethora of evidence has supported the consideration of RT in the salvage setting following failure of CAR T-cell therapy. Potential roles of RT to circumvent barriers faced by CAR T-cell therapy and/or orchestrate CAR T-cell response include (i) overcoming the immunosuppressive cells in the tumor microenvironment,[14,15] (ii) radiosensitizing tumor cells by upregulating specific chemokines, which appears to help trafficking of CAR T cells to infiltrate the tumor microenvironment,[26,27] (iii) inducing various tumor-associated antigens expression such as major histocompatibility complex class I, resulting in eliciting antitumor responses,[34–36] (iv) modulating CAR T cells to reestablish the appropriate memory T-cell phenotype,[3,12,13] and/or (v) reinvigorating CAR T cells after T-cell exhaustion or senescence.[7–9]

Using allogeneic SCT as a consolidative strategy following CAR T-cell therapy infusion has been previously explored in patients with acute lymphoblastic leukemia.[37–41] In lymphoma, RT has shown clear roles in the peri-transplant setting for patients with rel/ref LBCL. In patients with localized refractory LBCL, pretransplant RT can cytoreduce local residual fluorodeoxyglucose-avid disease thereby producing a complete metabolic response pre-autologous HSCT.[42–44] In our study, four of five patients who received RT in the peri-transplant setting entered a CR with RT, allowing them to proceed with allogeneic HSCT. Similarly, Imber *et al*. presented three patients who had local relapses at time of CAR T-cell failure, received bridging RT prior to allogeneic HSCT, and had no evidence of disease at the time of the last follow-up. These early favorable outcomes highlight the need to continue to study this combination as a salvage strategy in selected patients with CAR T-cell treatment failure.

Our patterns of failure analysis showed 97 of 124 (78%) patients progressed or relapsed in previously involved sites pre-CAR T. Imber *et al*.[17] reported on 11 of 14 (79%) patients who received RT to previously fluorodeoxyglucose-avid sites pre-CAR T. Figura *et al*.'s[18] subset analysis showed

that 31 of 36 progressions (86%) involve a component of local failure before CAR T-cell therapy infusion. Similarly, Saifi and colleagues[45] revealed that 57 of 65 (88%) post-CAR T failures occurred in sites of prior involvement.

Together, these findings highlight the potential therapeutic significance of incorporating RT pre-and/or post-CAR T-cell therapy infusion to provide local control and optimize outcomes. Small number of local failures and selection bias likely makes it difficult to show a significant association between bulk and local control, but this warrants further study. While we found a dose-response relationship favoring higher doses for improved OS, only one comprehensively treated patient received low dose RT and only three comprehensively treated patients had >1 site of disease. As such, those receiving higher doses had lower burden of disease, which likely also led to more favorable outcomes.

Early evidence from the pivotal CAR T trials and real-world studies suggested that patients with high tumor burden are more likely to experience inferior survival outcomes and lower durable remission rates following CAR T-cell therapy.[1,2,10,46] Moreover, surrogate tumor biomarkers such as LDH pre-CART have been proven to be promising tools in predicting outcomes post-CAR T.[46–50] However, prognostic factors at the time of CAR T-cell treatment failure have yet to be undefined. In our multicenter retrospective analysis of risk factors at the time of salvage therapy, we demonstrated that the presence of bulky disease (≥5 cm), presence of ≥2 sites of disease (nodal and/or extranodal), elevated LDH, stage 3-4 disease, and high IPI (≥3) status were identified to be prognostic markers for worse OS2 and EFS2; though elevated LDH, and advanced-stage disease portended the poorest OS2 and EFS2 in multivariate analyses. Hence, our data provide the rationale for the implementation of risk-stratification models by incorporating treatment biomarkers and baseline risk factors at the time of CAR T-cell treatment failure for predicting patients' outcomes in future studies.

There are several limitations of our study. The overwhelming majority in the salvage RT group received RT sequentially or concurrently with systemic regimens, precluding our ability to estimate the out-of-field recurrence rates post-RT on the post-RT imaging to ascertain if the out-field response was attributed to the effect of RT, systemic regimens, or both. Our findings are also limited by its retrospective nature and heterogeneity in RT dose/fractionation which was largely based on the extent of the disease.

Conclusion

CAR T-cell therapy holds great promise for rel/ref LBCL patients who would otherwise have poor outcomes, yet failure of CAR T-cell therapy is a pivotal challenge. Our data shows that disease burden and surrogate tumor biomarkers such as LDH at the time of CAR T-cell failure are associated with prognosis. RT is a feasible and promising therapeutic strategy that can provide local control, particularly in selected patients with limited-stage disease, and are able to receive comprehensive RT field. Small number of local failures and selection bias may have limited analysis regarding a dose-response relationship or an association with bulk.

Disclosures

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Contributions

HSA, CGP, and CAJ conceived and designed the study and wrote the manuscript. CGP, and CAJ provided supervision. All authors interpreted data, and contributed to revising the manuscript, and approved the submitted version.

Data-sharing statement:

The data generated in this study are not publicly available due to information that could compromise patient privacy or consent.

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