Consolidative radiotherapy for residual fluorodeoxyglucose activity on day +30 post CAR T-cell therapy in non-Hodgkin lymphoma

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Abstract

Majority of non-Hodgkin lymphoma (NHL) patients who achieve partial response (PR) or stable disease (SD) to CAR T-cell therapy (CAR T) on day +30 progress and only 30% achieve spontaneous complete response (CR). This study is the first to evaluate the role of consolidative radiotherapy (cRT) for residual fluorodeoxyglucose (FDG) activity on day +30 post-CAR T in NHL. We retrospectively reviewed 61 patients with NHL who received CAR T and achieved PR or SD on day +30. Progression-free survival (PFS), overall survival (OS), and local relapse-free survival (LRFS) were assessed from CAR T infusion. cRT was defined as comprehensive - treated all FDG-avid sites - or focal. Following day +30 positron emission tomography scan, 45 patients were observed and 16 received cRT. Fifteen (33%) observed patients achieved spontaneous CR, and 27 (60%) progressed with all relapses involving initial sites of residual FDG activity. Ten (63%) cRT patients achieved CR, and four (25%) progressed with no relapses in the irradiated sites. The 2-year LRFS was 100% in the cRT sites and 31% in the observed sites (P<0.001). The 2-year PFS was 73% and 37% (P=0.025) and the 2-year OS was 78% and 43% (P=0.12) in the cRT and observation groups, respectively. Patients receiving comprehensive cRT (n=13) had superior 2-year PFS (83% *vs*. 37%; P=0.008) and 2-year OS (86% *vs*. 43%; P=0.047) compared to observed or focal cRT patients (n=48). NHL patients with residual FDG activity following CAR T are at high risk of local progression. cRT for residual FDG activity on day +30 post-CAR T appears to alter the pattern of relapse and improve LRFS and PFS.

Introduction

Aggressive relapsed and/or refractory (r/r) B□cell non-Hodgkin lymphoma (NHL) remains a significant therapeutic challenge with poor outcomes. Anti-CD19-directed chimeric antigen receptor T-cell therapies (CAR T) are approved for treatment of r/r B-cell NHL, specifically large B-cell lymphoma, mantle cell lymphoma and follicular lymphoma. CAR T has demonstrated an objective response rate of 46% to 86%, and complete response rate of 28% to 66% for refractory large B-cell subtype.[1-5] However, sustained CAR T efficacy is limited, with durable complete response (CR) rates of approximately 40%.[1,6] Furthermore, up to 30% of NHL patients achieve a partial response (PR) or stable disease (SD) to CAR T on day +30, with most patients experiencing disease progression, specifically those with Deauville score (DS) 4-5.[7] Only 20% to 30% of PR/SD patients achieve spontaneous CR by day +90 without additional therapies.[1] Patients who progress post-CAR T have poor overall survival (OS).[8] Therefore, innovative consolidative strategies for this population are needed to augment disease control and prevent relapses. There is compelling rationale to consider consolidative radiotherapy (cRT) for post□CAR T disease. Patients who receive CAR T usually have purported chemoresistant but radiosensitive disease.[9] The predominant pattern of relapse of NHL following CAR T involves a local component.[10,11] Consolidative RT to initial bulky sites, extranodal sites, and residual fluorodeoxyglucose (FDG)-avid disease has long proven to improve outcomes in pa-

tients with aggressive NHL.[12-14] Similarly, RT improves outcomes when offered as part of the peri-autologous stem cell transplant regimen, specifically for patients with bulky disease, limited sites of relapse, or partially responded disease.[15-19] RT has promising outcomes in the peri-CAR T settings as a bridging strategy. It helps control the disease during the CAR T manufacturing period, improve rates of CAR T infusion, and possibly augment local control.[10,20-23] In the salvage setting, RT has recently shown to improve survival outcomes for limited relapsed NHL post autologous stem cell transplant and CAR T.[18,24,25]

To date, no data exist on the optimal management of patients with residual FDG activity on day +30 post-CAR T. This study is the first to report on the role of consolidative RT for residual FDG activity (DS 4-5) on day +30 post-CAR T in B-cell NHL.

Methods

Following Institutional Review Board approval, records of consecutive patients diagnosed with r/r B-cell NHL who received CAR T and achieved PR or SD on day +30 were retrospectively studied across three institutions between 2018 and 2022. This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Ann Arbor staging system was used to define the number of involved/FDG-avid lymph node sites. Residual activity (RA) corresponded to patients with PR or SD who had FDG-avid (DS 4-5) sites on day +30. Only patients with ≤4 RA sites on day +30 post-CAR T were included. This number is based on a previous publication that defined post-CAR T limited relapsed disease.[18]

Bridging therapy (systemic or radiation) was defined as treatment administered between leukapheresis and lymphodepleting chemotherapy. Remote radiotherapy was defined as RT administered >30 days from CAR T infusion. Consolidative systemic therapy was defined as chemo/immuno/transplant therapy administered following day +30 post-CAR T for RA. cRT was defined as RT delivered following day +30 post-CAR T for RA. Comprehensive cRT was defined as treating all residual FDG-avid sites identified on day +30. Focal cRT was defined in cases where not all residual FDG-avid sites were treated. RT was at the discretion of the treating physician and consisted of positron emission tomography (PET)-directed residual site radiotherapy (PD-RSRT) or involved site radiotherapy (ISRT). RT-related toxicities were graded prospectively per the Common Terminology Criteria for Adverse Events version 5 (CTCAE v.5). The RT equivalent 2 Gy dose was calculated based on an α/β ratio of 10.

Following the management approach on day +30, response to treatment was assessed on day +90-100 with a PET/computed tomography (PET/CT) scan using the Lugano criteria.[26] Subsequent imaging were performed for assessment of response or lack thereof. CR was defined as a DS of 1-3, PR/SD were defined as a DS of 4-5 with absence of disease progression, and progression of disease (PD) was defined as a DS of 4-5 following a CR/PR. Local response of individual RA sites was assessed based on careful review of the location of RA sites identified on day +30 PET/CT scan and their response on subsequent imaging.

Statistical analysis was performed using IBM SPSS 28.0 software. Continuous data were reported as medians and ranges. Categorical data were reported as frequencies and percentages. Comparisons of different characteristics between the two groups were done using X^2 and Fisher's exact tests. The non-parametric independent samples median test was used to compare median values between two groups. Progression-free survival (PFS), overall survival (OS), and local relapse-free survival (LRFS) were estimated by Kaplan-Meier survival curves. Survival differences were assessed by the log-rank test. All reported *P* values were two-sided, and differences were considered statistically significant at $P<0.05$.

The median follow-up period was calculated from the CAR T infusion date to the last documented follow-up visit. LRFS was calculated based on the total number of RA sites and was defined from CAR T infusion to local relapse (LR) in the RA site identified on day +30. PFS was defined from CAR T infusion to any local/distant disease progression. OS was defined from CART infusion to death.

Results

Management approach on day +30 post-CAR T

Sixty-eight patients were identified with B-cell NHL who achieved PR or SD to CAR T with residual FDG activity on day +30 between 2018 and 2022. Among those, 61 patients had ≤4 residual FDG-avid sites and met our inclusion criteria, and seven patients had ≥5 residual FDG-avid sites and were excluded. Only one patient had biopsy proven persistent disease and the rest were unbiopsied and classified as having RA based on radiological assessment. Following day +30 PET/CT scan, 45 patients with RA were observed and 16 received cRT. Only one patient received consolidative systemic therapy (polatuzumab vedotin combined with bendamustine and rituximab) and belonged to the cRT group. The median follow-up from CAR T infusion was 21 months for the entire cohort.

Baseline characteristics

The median age of the cohort was 62 (range, 18-85) years, and the maximum number of residual FDG-avid sites per patient identified on day +30 post-CART was three. There

Table 1. Pre-CAR T and day +30 post-CAR T baseline characteristics.

	Management on day +30 post-CAR T			
	Observation (N=45)	**Consolidative radiotherapy (N=16)**	**Total (N=61)**	***P***
Baseline characteristics at time of CAR T infusion				
Age in years Median (range)	62 (18-82)	61 (33-85)	62 (18-85)	0.49
Sex, N (%) Female Male	13 (28.9) 32 (71.1)	5 (31.3) 11 (68.7)	18 (29.5) 43 (70.5)	0.86
Histology, N (%) DLBCL FL HGBCL MCL PMBCL	39 (86.7) 0 (0) 5 (11.1) 0 (0) 1 (2.2)	14 (87.5) 1 (6.3) 0 (0) 1 (6.3) 0 (0)	53 (86.9) 1 (1.6) 5 (8.2) 1 (1.6) 1 (1.6)	0.1
Disease stage, N (%) Advanced Limited	17 (37.8) 28 (62.2)	9 (56.3) 7 (43.8)	26 (42.6) 35 (57.4)	0.2
Extranodal involvement, N (%) No Yes	29 (64.4) 16 (35.6)	7 (43.8) 9 (56.3)	36 (59.0) 25 (41.0)	0.15
Previous lines of therapy, N Median (range)	2 (1-4)	2 (1-7)	2 (1-7)	0.47
Biggest tumor size, cm Median (range)	7.3 (1.1-20)	4.5 (2-17.1)	6.8 (1.1-20)	0.21
Highest SUV_{max} Median (range)	17.6 (3.2-42.2	17.5 (2.7-38.1)	17.6 (2.7-42.2)	0.51
LDH level, mU/mL Median (range)	232 (127-669)	218 (150-470)	228 (127-669)	0.2
CRP level, mg/L Median (range)	11.6 (1-160.9)	12.55 (1-75.1)	11.6 (1-160.9)	0.95
Bridging chemotherapy, N (%) No Yes	30 (66.7) 15 (33.3)	12 (75) 4 (25)	42 (68.9) 19 (31.1)	0.54
Bridging radiotherapy, N (%) No Yes	36 (80) 9 (20)	12 (75) 4 (25)	48 (78.7) 13 (21.3)	0.68
Baseline characteristics on day +30 post-CAR T				
# Residual FDG-avid sites, N Median (range)	1 (1-3)	2 (1-3)	1 (1-3)	0.007
RA site size, cm Median (range)	2.6 (0.7-16)	1.8 (0.5-14)	2 (0.5-16)	0.054
RA site SUV_{max} Median (range)	5.1 (2.4-38.2)	5.2 (2.0-32.0)	5.1 (2.0-38.2)	0.77
RA site SUV_{max}>10, N (%) No Yes	49 (76.6) 15 (23.4)	20 (74.1) 7 (25.9)	69 (75.8) 22 (24.2)	0.8
Deauville score, N (%) 4 5	36 (80) 9 (20)	14 (87.5) 2 (12.5)	50 (82) 11 (18)	0.5
LDH level, mU/mL Median (range)	205 (141-623)	194.5 (144-436)	200 (141-623)	0.28
CRP level, mg/L Median (range)	2.9 (1-163.7)	1 (1-14.5)	1.95 (1-163.7)	0.58

CAR T: anti-CD19-directed chimeric antigen receptor T-cell therapy; DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; HGBCL: high grade B-cell lymphoma; MCL: mantle cell lymphoma; PMBCL: primary mediastinal B-cell lymphoma; SUV_{max}: maximum standardized uptake volume; LDH: lactate dehydrogenase; CRP: C-reactive protein; FDG: fluorodeoxyglucose; RA: residual activity.

were no significant differences in the pre-CAR T baseline characteristics between patients who received cRT and those who did not. Prior to CAR T, bridging RT was given to 13 patients (9 in observation group and 4 in cRT group) and bridging chemotherapy was given to 19 patients (15 in observation group and 4 in cRT group). The residual FDG-avid sites on day +30 were radiation-naïve in 48 patients (34 in observation group and 14 in cRT group), received remote RT in four patients (3 in observation group and 1 in cRT group), and received bridging RT in nine patients (8 in observation group and 1 in cRT group). There were no significant differences in the day +30 baseline characteristics, including the median size and maximum standardized uptake volume (SUV_{max}) of the residual FDG-avid sites, between the two groups. However, the median number of residual FDG-avid sites on day +30 was higher in the cRT group (2 *vs*. 1; *P*=0.007). Further baseline disease specific, patient specific, and treatment specific characteristics are listed in Table 1.

Consolidative radiotherapy

The median equivalent 2 Gy (EQD2) dose for cRT was 39.1 (interquartile range [IQR], 39.1-40) Gy, and the most common cRT regimen was 37.5 Gy in 15 fractions. The target sites included the abdomen (n=8), axilla (n=5), head and neck (n=5), pelvis (n=4), skeleton (n=3) and mediastinum/thorax (n=2). The median size and SUV_{max} of the irradiated sites with residual activity were 2.5 (range, 0.5-14) cm, and 5.2 (range, 2-32), respectively. Six residual FDG-avid sites consolidated with cRT were extranodal (skeleton n=3, soft tissue/muscles n=1, colon n=1, lung n=1). The median time between CART infusion and cRT initiation was 57 (range, 31-118) days. cRT was delivered through 3-dimentional (n=6), IMRT (n=9), or proton therapy (n=1) techniques. Thirteen patients were treated with PD-RSRT and three with ISRT. Comprehensive cRT was given to 13 patients and focal cRT was given to three patients. The number of residual FDG-avid sites in the comprehensive cRT patients ranged between one and three with all sites receiving cRT to a median EQD2 dose of 39.1 Gy. The number of residual FDG-avid sites in the focal cRT patients ranged between two and three with only one site per patient receiving cRT. Focal cRT was delivered to a definitive dose of ≥40 Gy EQD2 in two patients and to a palliative dose of 12 Gy EQD2 in one patient. The unirradiated residual FDG-avid sites in the focal cRT patients did not receive prior remote or bridging RT. One patient received cRT (proton SBRT 39 Gy in 3 fractions) to a site with residual activity that was previously irradiated in the bridging setting (37.5 Gy in 10

Table 2. Baseline and radiation treatment characteristics of patients consolidated with radiotherapy.

Patient #	Number of previous lines of therapy	Disease stage pre-CAR T	Day +30 response	Number of FDG-avid sites on day +30	Type of cRT	Number of irradiated sites	RT dose (Gy)	RT fractions	Sites response to cRT	Patient ultimate overall response to CAR T and cRT	RT in-field recurrence	Local recurrence in the residual FDG-avid site(s)	Progression
1	3	Advanced	PR	2	Focal	1	30	5	CR	PD	No	Yes	Yes
2	7	Advanced	PR	3	Focal	1	8	1	CR	PD	No	Yes	Yes
3	2	Advanced	SD	2	Focal	1	50	20	PR	PR	No	No	No
4	2	Limited	SD	1	Comp	1	45	18	CR	CR	No	No	No
5	2	Limited	PR	1	Comp	1	39	3	CR	CR	No	No	No
6	2	Limited	PR	2	Comp	2	40	20	CR	CR	No	No	No
7	4	Advanced	PR	3	Comp	3	37.5	15	CR	CR	No	No	No
8	2	Advanced	PR	3	Comp	3	40	20	CR	CR	No	No	No
9	3	Limited	SD	2	Comp	2	20	10	PR	PR	No	No	No
10	3	Limited	SD	1	Comp	1	8	2	CR	CR	No	No	No
11	2	Limited	PR	1	Comp	1	20	5	CR	CR	No	No	No
12	1	Limited	PR	2	Comp	2	44	25	CR	CR	No	No	No
13	2	Advanced	PR	2	Comp	2	44	22	CR	CR	No	No	No
14	2	Advanced	PR	2	Comp	2	37.5	15	CR	PD	No	No	Yes
15	2	Advanced	PR	3	Comp	3	37.5	15	CR	PD	No	No	Yes
16	1	Advanced	PR	1	Comp	1	30	5	CR	CR	No	No	No

CAR T: anti-CD19-directed chimeric antigen receptor T-cell therapy; PR: partial response; SD: stable disease; CR: complete response; PD: progression of disease; FDG: fluorodeoxyglucose; cRT: consolidative radiotherapy; comp: comprehensive; RT: radiotherapy; Gy: Gray.

fractions). Nine patients had grade zero, three patients had grade 1 (fatigue, pharyngitis, xerostomia), and four patients had grade 2 (fatigue, pharyngitis/esophagitis, xerostomia, nausea, diarrhea, dermatitis) RT-related toxicities. There were no grade 3 or higher RT-related toxicities in this cohort. None of the patients developed a flare of cytokine release syndrome following cRT. Detailed description of the 16 cRT patients is provided in Table 2.

Local response

A total of 91 sites with RA were identified on day +30 post-CAR T; 64 were observed and 27 received cRT. Sustained CR was achieved in 14 (22%) observed sites without additional therapies compared to 24 (92%) sites consolidated with RT (P<0.001). Forty-two (66%) observed sites experienced LR, while no cRT sites relapsed (P<0.001). The 2-year LRFS was 100% in the cRT sites and 31% in the observed sites (P<0.001) (Figure 1). Fifteen disease sites (11 in observation group and 4 in cRT group) corresponding to 13 patients received bridging RT prior to CART. Only three (20%) bridged sites (3 in observation group and 0 in cRT group) corresponding to three patients experienced local relapse in the bridging radiation field. Among the aforementioned BRT sites, nine (8 in observation group and 1 in cRT group) were identified on day +30 with RA, and three (33%) experienced disease progression.

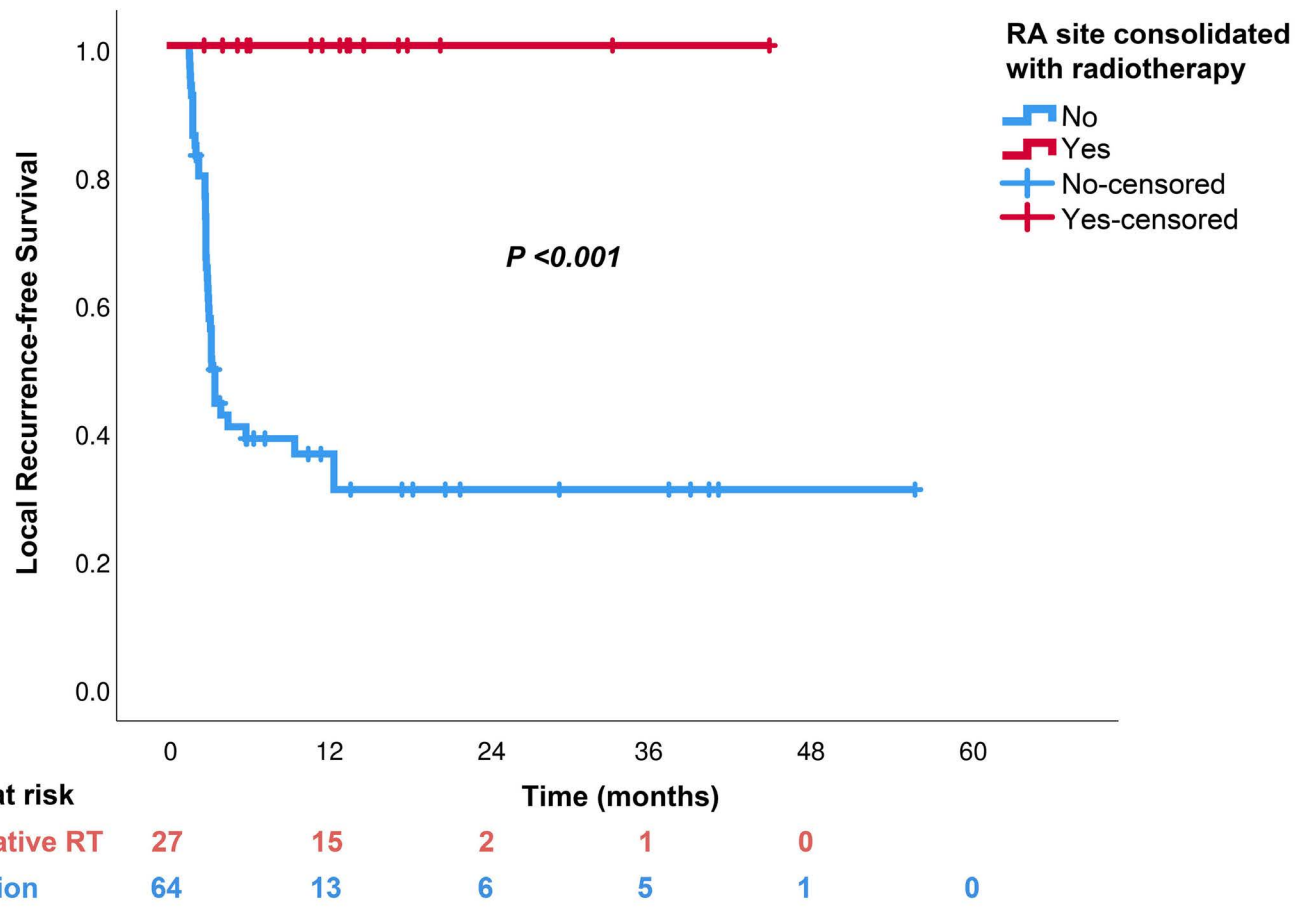

Figure 1. Local recurrence-free survival by receipt of consolidative radiation to individual sites. RA: residual activity; RT: radiotherapy.

Table 3. Disease progression stratified by the number of sites with residual fluorodeoxyglucose activity and management approach on day +30 post-CAR T.

Number of sites with residual activity on day +30 post-CAR T (N)	Management approach on day +30 post-CAR T (N)	Disease progression N (%)	*P*
One site with residual activity (38 patients)	Observation (33) RT (5)	17 (51.5) 0 (0)	0.031
Two sites with residual activity (13 patients)	Observation (6) RT (7)	5 (83) 2 (29)	0.048
Three sites with residual activity (10 patients)	Observation (6) RT (4)	5 (83) 2 (50)	0.26

CAR T: anti-CD19-directed chimeric antigen receptor T-cell therapy; RT: radiotherapy.

Patients' outcomes and pattern of relapse

Among the observed patients, 15 (33%) achieved spontaneous CR without additional therapies with two of 15 subsequently relapsing, five (11%) remained with PR/SD, and 27 (60%) experienced disease progression with all relapses involving the original sites of residual activity. Among patients who received cRT, ten (63%) achieved CR, two (12%) achieved a PR, and four (25%) had disease progression with no relapses in the irradiated sites. The relapses (n=2) in the comprehensive cRT patients were out-of-field and involved new sites that were not present on day +30. The relapses (n=2) in the focal cRT patients involved the original sites with RA that were present on day +30 but did not get irradiated. None of the ten cRT patients achieving CR relapsed or required subsequent therapies. The effect of cRT was most prominent in pa-

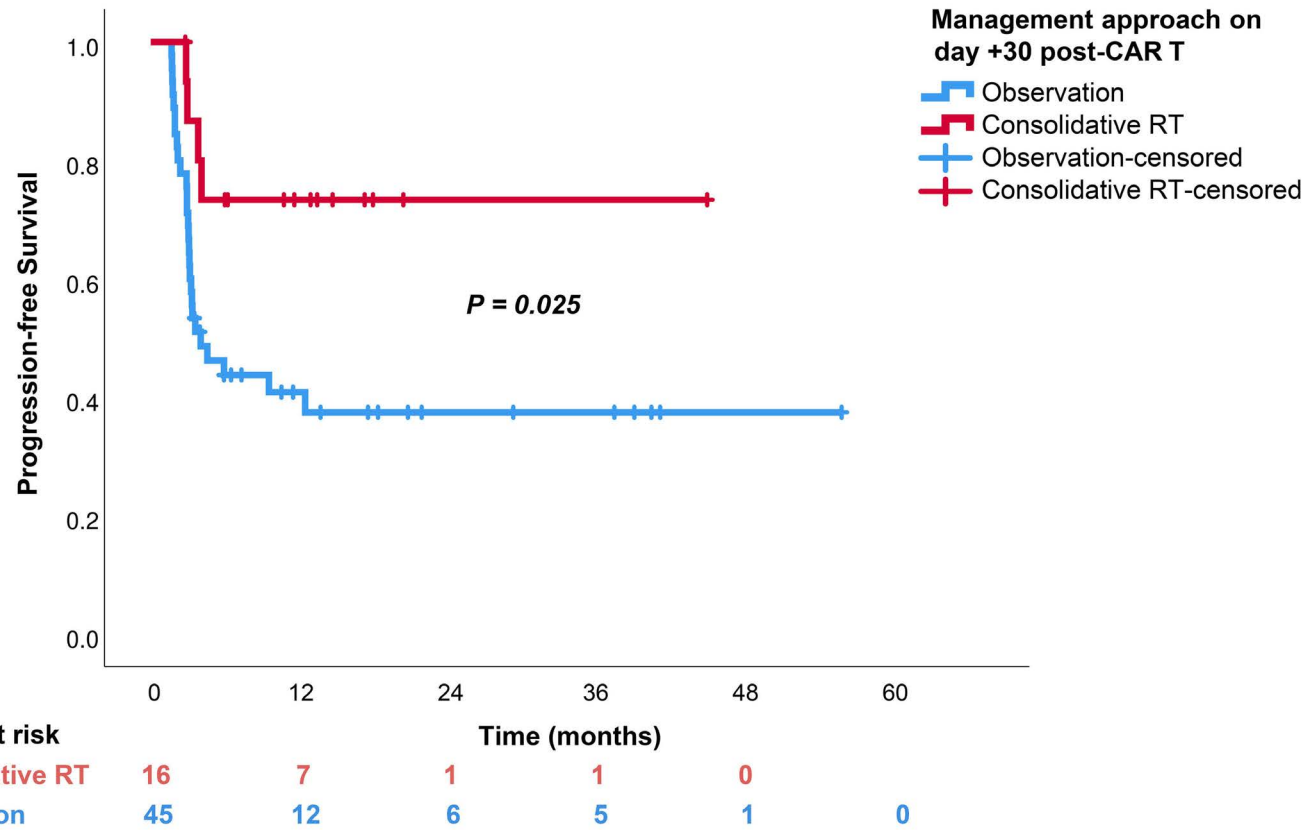

Figure 2. Progression-free survival by management approach on day +30. CAR T: anti-CD19-directed chimeric antigen receptor T-cell therapy; RT: radiotherapy.

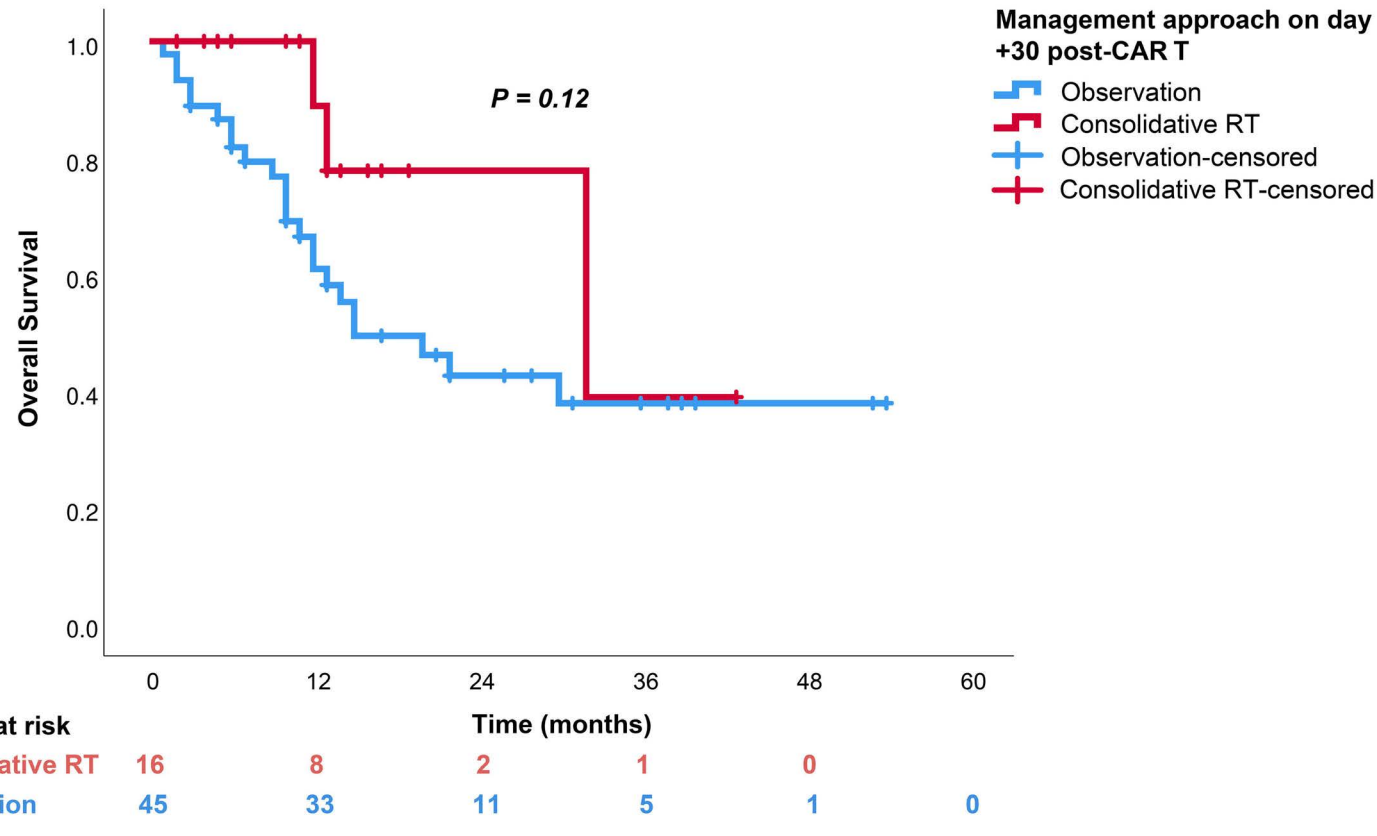

Figure 3. Overall survival by management approach on day +30. CAR T: anti-CD19-directed chimeric antigen receptor T-cell therapy; RT: radiotherapy.

tients with ≤2 residual FDG-avid sites on day +30, especially in those with only one FDG-avid site post-CAR T (Table 3).

The 2-year PFS was 73% in the cRT group and 37% in the observation group (*P*=0.025) (Figure 2). The 2-year OS was 78% in the cRT group and 43% in the observation group (*P*=0.12) (Figure 3). Patients consolidated with comprehensive cRT to all residual FDG-avid sites (n=13) had superior 2-year PFS (83% *vs*. 37%; *P*=0.008) (Figure 4) and 2-year OS (86% *vs*. 43%; *P*=0.047) (Figure 5) compared to those who were observed or received focal cRT to some but not all residual FDG-avid sites (n=48).

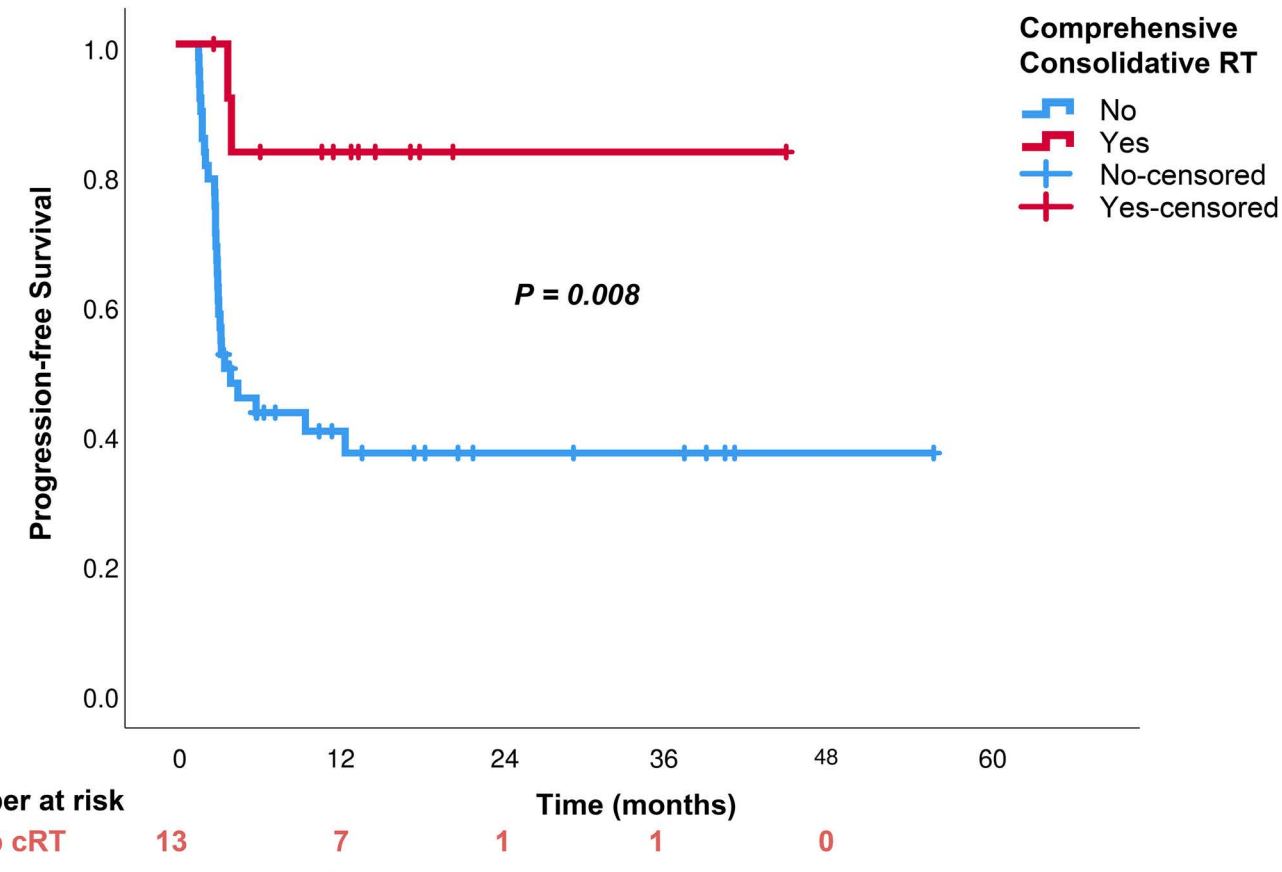

Figure 4. Progression-free survival by receipt of comprehensive consolidative radiotherapy. Comp: comprehensive; cRT: consolidative radiotherapy.

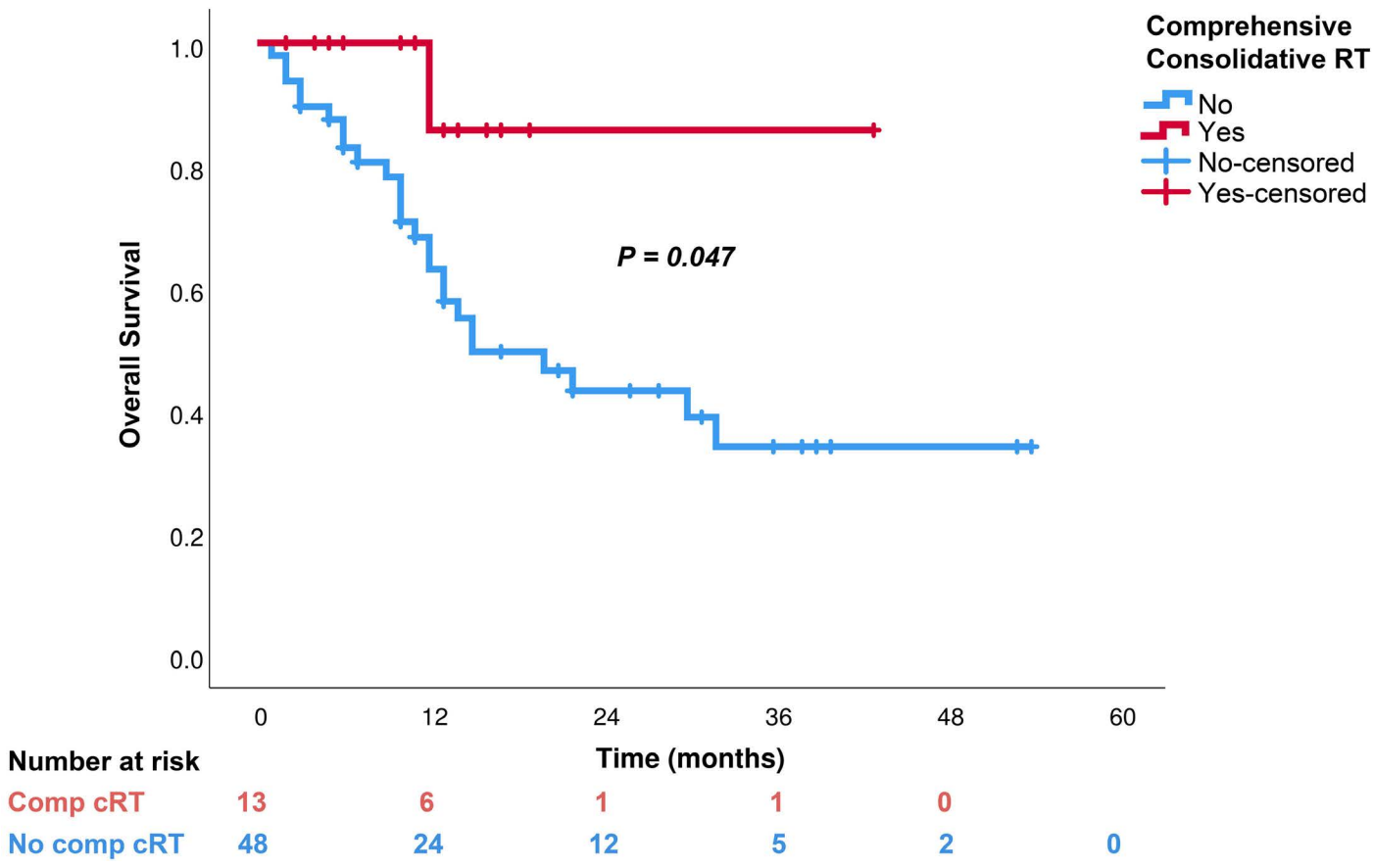

Figure 5. Overall survival by receipt of comprehensive consolidative radiotherapy. Comp: comprehensive; cRT: consolidative radiotherapy.

Discussion

This study is the first to report on the role of consolidative radiotherapy for residual FDG activity on day +30 post-CART in B-cell NHL. Despite the small sample size and relatively short follow-up period, patients with residual activity who received cRT had significantly better outcomes with minimal added toxicity compared to those who were observed on day +30 post-CAR T. In our cohort, patients who achieved a PR or SD to CAR T on day +30 and were observed, had a high risk of disease progression with a predominant localized pattern of relapse. However, cRT following day +30 altered the pattern of relapse, as evident with the absence of relapses in the irradiated FDG-avid sites. Such alteration in the pattern of relapse resulted in a local recurrence-free survival benefit which translated to an improvement in PFS. Such PFS benefit is promising and may result in an encouraging OS when all residual FDG-avid sites are consolidated with radiotherapy (comprehensive cRT).

The current most likely adopted management approach for patients with residual activity/disease on day +30 post-CAR T is observation. This is based on the ZUMA-1 trial findings that showed a 20% to 30% conversion rate of PR/SD to CR without additional therapies,[1] which coincides with the spontaneous conversion rate (33%) seen in our cohort. Thus, the ZUMA-1 trial concluded that it would be reasonable to monitor PR/SD patients to allow for an opportunity for an improved response, since consolidation with allogenic stem cell transplantation comes with a high rate of treatment-related death and would ablate CAR T cells.[1] Yet, this recommendation ignores the fact that 70% to 80% of PR/SD patients will likely progress and that cRT can be an effective and minimally toxic consolidative treatment option, as we have shown in this study. This is further supported by Kuhnl *et al*. who showed that patients with a DS of 4-5 on day +30 have a high risk of relapse and shorter duration of response which calls for risk-adaptive treatment approaches for these patients to prevent/delay progression.[7]

The utility of cRT can be further supported by understanding the pattern of relapse of NHL following CAR T. Previous studies have shown >85% of post-CAR T relapses involve a local component.[10,11] Such pattern of local relapse is more evident in those who achieve a PR/SD to CAR T, as 100% of the relapses in our observed cohort involved the sites with RA that were originally present prior to CAR T. The local relapse component has also been significantly present but to a lesser extent (40-60%) in the frontline setting as evident by multiple seminal studies that established the standard of care for NHL.[27-30] This might suggest an increase in localized chemorefractory disease in the r/r setting following multiple lines of therapies, where persistent gross disease, not ablated by initial therapies, may be less responsive to new systemic treatments and more likely to relapse. This calls for local therapies to augment local control in the r/r setting, and intriguingly, none of the radiated FDG-avid sites in our cohort relapsed.

The role of local therapy becomes more noticeable and valuable as we move forward in understanding and defining oligometastatic lymphoma. This can be inferred from the improved outcomes seen with stereotactic body radiotherapy (SBRT) when offered as a consolidative local therapy for oligometastatic solid malignancies.[31,32] Our study included only patients with ≤4 residual FDG-avid sites based on a previous publication,[18] and not based on any evidence-base for the utility/benefit of RT. That study suggested comprehensive RT to be feasible for ≤4 lymphoma disease sites with improvement in survival metrics[18], and thus formed the basis to our inclusion criteria. From an oligometastatic standpoint, the impact of cRT in our cohort was mostly evident in patients with ≤2 residual FDG-avid sites, especially in those with only one site on day +30 post-CAR T (Table 3). While acknowledging the limited number of patients with >2 FDG-avid sites (n=10) in our study, the tumor burden, and the decreased feasibility of comprehensive cRT with increasing number of FDG-avid sites, one might consider adding consolidative systemic therapy to cRT for patients who have multiple sites of RA on day +30 post-CAR T. Furthermore, it is important to acknowledge that patients with one residual FDG-avid site have less tumor burden and will fall under the comprehensive cRT subcohort by default if they receive cRT. This may limit comparisons between focal and comprehensive cRT subgroups if tumor burden is not accounted for. Moreover, it was noted in our study (Table 3) that cRT was more likely to be offered to patients with >1 RA site, as the perception for 1 RA site is perhaps to resolve spontaneously. Intriguingly, 51.5% of patients with 1 RA site who were observed relapsed. All relapses had a local component and involved the same RA site identified on day +30, rationalizing the use of local therapy, such as RT, that showed to be effective for these patients in our study.

Radiation has long proven to be a successful and effective consolidative treatment for aggressive NHL in the frontline and r/r setting. As part of a combined modality therapy in the upfront setting, consolidative radiotherapy improves outcomes compared to chemotherapy alone.[30,33] This is mostly evident in patients with bulky disease,[12,34] extranodal involvement,[14] and residual partially responded disease.[35,36] Compellingly, patients with PR who receive cRT have comparable survival outcomes to those who achieve CR to systemic therapy.[35-37] In the r/r setting, peri-transplant RT augments local control and improves outcomes when offered as a consolidative therapy pre- or post-stem cell transplant.[17,38-45] For limited relapsed (1 site) post-transplant disease, salvage RT improves OS compared to

salvage chemotherapy.[24] Studies supporting the utility of RT in the peri-CAR T setting are more limited but have promising outcomes. RT was mostly studied in the bridging setting prior to CAR T and has shown to be safe and effective in controlling the disease during the manufacturing period with favorable local control rates that can augment the efficacy of CAR T.[10,18,19,21-23,46] More recently, it was shown that comprehensive salvage RT for limited (≤4 disease sites) post-CAR T relapsed disease improves survival,[18,25] supporting the utility of RT for oligoprogressive post-CAR T lymphoma. However, no studies investigated the utility of RT as a consolidative therapy following CAR T for residual non-progressive disease. Given the aforementioned reasons, RT was adopted in the participating institutions as a consolidative management approach on day +30 post-CAR T, with very favorable outcomes as reported in the results section.

Utilizing RT in the bridging pre-CAR T or consolidative post-CAR T setting remains inconclusive. Eleven (24%) patients in our observation group received prior RT (3 remote RT and eight bridging RT) which might have precluded them from getting additional consolidative radiation on day +30, contemplating the optimal timing of peri-CAR T radiotherapy. However, four (25%) patients in our cRT cohort received bridging RT prior to CAR T, suggesting the feasibility of administering RT pre- and post-CAR T if needed. This was more achievable if the residual FDG-avid sites on day +30 were not radiated in the bridging or remote setting.

Some concerns arise on whether an early administration of RT on day +30 may have an impact on circulating CAR T cells. There are no data yet to support or refute this argument, however, the favorable outcomes of our cohort suggest the safety of cRT with no obvious detrimental effect on CART. Animal studies have shown radiation to increase the efficacy of CART and perhaps induce and abscopal-like effect.[47-49] A recent study showed a plausible synergistic effect of RT with CAR T, and there may be an optimal timing to deliver RT during peri-CAR T.[18] Plausibly, RT when administered approximately 30 days following CAR T, may sensitize and reactivate CAR T cells. Studies investigating the impact of RT on circulating CAR T cells and released cytokines are needed.

This study is limited by its retrospective nature and the relatively small sample size, especially in the cRT cohort. RT was delivered at the discretion of the treating radiation oncologist with no standardized dosing and fractionation regimens. There were no clear indications for referring patients to receive cRT and the decision was at the discretion of the treating hematologist. Furthermore, the majority of patients (98%) did not get a biopsy to confirm the FDG-avidity is actually reflective of persistent lymphoma, and, therefore, it would not be possible to tell how many patients had true persistent disease *versus* inflammatory changes in both cohorts. Some patients with RA may spontaneously convert to CR, either due to the resolution of FDG-avid inflammatory changes, or due to the continued activity of CAR T cells against residual lymphoma. In these particular scenarios, which are difficult to identify/quantify, the addition of radiation may seem to be unnecessary. Therefore, identifying patients with RA at risk of progression is important to select the right management approach, and this was mostly based on clinical and radiological assessment in our study. Studies suggested that patients with SUV_{max}>10 on day +30,[50] and DS of 4-5[7] have higher risk of progression, and, therefore, may be used as parameters to identify patients who may benefit from consolidative treatments. Nonetheless, the detrimental outcome of post-CAR T relapses calls for maximal utility of upfront peri-CAR T treatments, and consolidative radiotherapy appeared to be highly effective and minimally toxic in our cohort. Also, it is important to acknowledge the short follow-up period in cRT cohort, as evident in the Kaplan-Meier curves, given the recent adoption of this management approach by the participating institutions. Longer follow-up is needed to confirm the response durability to cRT. Finally, despite the absence of significant differences in baseline characteristics between both cohorts, there might be other unaccounted confounding factors

Conclusion

Patients with B-cell NHL who achieve PR or SD by PET to CAR T are at high risk of local progression. cRT for residual FDG activity on day +30 post-CAR T appears to alter the pattern of relapse and improve local recurrence-free survival and PFS. Comprehensive cRT further improves PFS and results in promising overall survival outcomes. An equivalent 2 Gy dose of 39-40 Gy seems sufficient to provide excellent local control with low toxicity. Longer follow-up and larger multicenter prospective studies are needed to confirm our findings.

Disclosures

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Contributions

OS, JLP and BSH concveived and designed the study. OS, JLP, BSH, MAKD, YL and WGB provided study materials or patients. OS, WGB, RB, JLP, BSH and MAKD collected and assembled data. OS, JLP, BSH and MAKD analyzed and interpreted data. All authors wrote the manuscript, gave the final approval of the manuscript and are accountable for all aspects of the work.

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Data-sharing statement

All relevant data are available in the article, Online Supplementary Appendix or from the corresponding author upon reasonable request.

References

1. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med. 2017;377(26):2531-2544.
2. Abramson JS, Palomba ML, Gordon LI, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. Lancet. 2020;396(10254):839-852.
3. Schuster SJ, Tam CS, Borchmann P, et al. Long-term clinical outcomes of tisagenlecleucel in patients with relapsed or refractory aggressive B-cell lymphomas (JULIET): a multicentre, open-label, single-arm, phase 2 study. Lancet Oncol. 2021;22(10):1403-1415.
4. Locke FL, Miklos DB, Jacobson CA, et al. Axicabtagene ciloleucel as second-line therapy for large B-cell lymphoma. N Engl J Med. 2022;386(7):640-654.
5. Bishop MR, Dickinson M, Purtill D, et al. Second-line tisagenlecleucel or standard care in aggressive B-cell lymphoma. N Engl J Med. 2022;386(7):629-639.
6. Nair R, Neelapu SS. The promise of CAR T-cell therapy in aggressive B-cell lymphoma. Best Pract Res Clin Haematol. 2018;31(3):293-298.
7. Kuhnl A, Roddie C, Kirkwood AA, et al. Early FDG-PET response predicts CAR-T failure in large B-cell lymphoma. Blood Adv. 2022;6(1):321-326.
8. Chow VA, Gopal AK, Maloney DG, et al. Outcomes of patients with large B-cell lymphomas and progressive disease following CD19-specific CAR T-cell therapy. Am J Hematol. 2019;94(8):E209-E213.
9. Martens C, Hodgson DC, Wells WA, et al. Outcome of hyperfractionated radiotherapy in chemotherapy-resistant non-Hodgkin's lymphoma. Int J Radiat Oncol Biol Phys. 2006;64(4):1183-1187.
10. Saifi O, Breen WG, Lester SC, et al. Does bridging radiation therapy affect the pattern of failure after CAR T-cell therapy in non-Hodgkin lymphoma? Radiother Oncol. 2022;166:171-179.
11. Figura NB, Robinson TJ, Sim AJ, et al. Patterns and predictors of failure in recurrent or refractory large B-cell lymphomas after chimeric antigen receptor T-cell therapy. Int J Radiat Oncol Biol Phys. 2021;111(5):1145-1154.
12. Held G, Murawski N, Ziepert M, et al. Role of radiotherapy to bulky disease in elderly patients with aggressive B-cell lymphoma. J Clin Oncol. 2014;32(11):1112-1118.
13. Poeschel V, Held G, Ziepert M, et al. Four versus six cycles of CHOP chemotherapy in combination with six applications of rituximab in patients with aggressive B-cell lymphoma with favourable prognosis (FLYER): a randomised, phase 3, non-inferiority trial. Lancet. 2019;394(10216):2271-2281.
14. Held G, Zeynalova S, Murawski N, et al. Impact of rituximab and radiotherapy on outcome of patients with aggressive B-cell lymphoma and skeletal involvement. J Clin Oncol. 2013;31(32):4115-4122.
15. Philip T, Armitage JO, Spitzer G, et al. High-dose therapy and autologous bone marrow transplantation after failure of conventional chemotherapy in adults with intermediate-grade or high-grade non-Hodgkin's lymphoma. N Engl J Med. 1987;316(24):1493-1498.
16. Ng AK, Yahalom J, Goda JS, et al. Role of radiation therapy in patients with relapsed/refractory diffuse large B-cell lymphoma: guidelines from the international lymphoma radiation oncology group. Int J Radiat Oncol Biol Phys. 2018;100(3):652-669.
17. Hoppe BS, Moskowitz CH, Filippa DA, et al. Involved-field radiotherapy before high-dose therapy and autologous stem-cell rescue in diffuse large-cell lymphoma: long-term disease control and toxicity. J Clin Oncol. 2008;26(11):1858-1864.
18. Saifi O, Breen WG, Lester SC, et al. Don't put the CART before the horse: the role of radiation therapy in peri-CAR T-cell therapy for aggressive B-cell non-Hodgkin lymphoma. Int J Radiat Oncol Biol Phys. 2023;116(5):999-1007.
19. Saifi O, Breen W, Lester SC, et al. The impact of radiation timing in peri-CAR T-cell therapy on local control for relapsed/refractory B-cell non-Hodgkin lymphoma. Int J Radiat Oncol Biol Phys. 2022;114(3):S85-S86.
20. Saifi O, Breen W, Lester S, et al. In-field recurrences in relapsed/refractory (R/R) B-cell non-Hodgkin lymphoma (NHL) bridged with radiation prior to CD19 chimeric antigen receptor T-cell therapy (CART). J Clin Oncol. 2022;40(Suppl 16):S7556-7556.
21. Sim AJ, Jain MD, Figura NB, et al. Radiation therapy as a bridging strategy for CAR T cell therapy with axicabtagene ciloleucel in diffuse large B-cell lymphoma. Int J Radiat Oncol Biol Phys. 2019;105(5):1012-1021.
22. Wright CM, LaRiviere MJ, Baron JA, et al. Bridging radiation therapy before commercial chimeric antigen receptor T-cell therapy for relapsed or refractory aggressive B-cell lymphoma.

Int J Radiat Oncol Biol Phys. 2020;108(1):178-188.
23. Pinnix CC, Gunther JR, Dabaja BS, et al. Bridging therapy prior to axicabtagene ciloleucel for relapsed/refractory large B-cell lymphoma. Blood Adv. 2020;4(13):2871-2883.
24. Ladbury C, Kambhampati S, Othman T, et al. Role of salvage radiation treatment of relapses in relapsed/refractory diffuse large B cell lymphoma post-autologous stem cell transplant. Int J Radiat Oncol Biol Phys. 2022;113(3):594-601.
25. Saifi O, Breen W, Lester SC, et al. Comprehensive salvage radiotherapy for limited relapsed B-cell non-Hodgkin lymphoma following CD19 chimeric antigen receptor T-cell therapy. Int J Radiat Oncol Biol Phys. 2022;114(3):S56.
26. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32(27):3059-3068.
27. Reyes F, Lepage E, Ganem G, et al. ACVBP versus CHOP plus radiotherapy for localized aggressive lymphoma. N Engl J Med. 2005;352(12):1197-1205.
28. Bonnet C, Fillet G, Mounier N, et al. CHOP alone compared with CHOP plus radiotherapy for localized aggressive lymphoma in elderly patients: a study by the Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol. 2007;25(7):787-792.
29. Lamy T, Damaj G, Soubeyran P, et al. R-CHOP 14 with or without radiotherapy in nonbulky limited-stage diffuse large B-cell lymphoma. Blood. 2018;131(2):174-181.
30. Horning SJ, Weller E, Kim K, et al. Chemotherapy with or without radiotherapy in limited-stage diffuse aggressive non-Hodgkin's lymphoma: Eastern Cooperative Oncology Group study 1484. J Clin Oncol. 2004;22(15):3032-3038.
31. Gomez DR, Blumenschein GR, Jr., Lee JJ, et al. Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study. Lancet Oncol. 2016;17(12):1672-1682.
32. Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy for the comprehensive treatment of oligometastatic cancers: long-term results of the SABR-COMET phase II randomized trial. J Clin Oncol. 2020;38(25):2830-2838.
33. Miller TP, Dahlberg S, Cassady JR, et al. Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-Hodgkin's lymphoma. N Engl J Med. 1998;339(1):21-26.
34. Pfreundschuh M, Murawski N, Ziepert M, et al. Radiotherapy (RT) to bulky (B) and extralymphatic (E) disease in combination with 6xR-CHOP-14 or R-CHOP-21 in young good-prognosis DLBCL patients: results of the 2x2 randomized UNFOLDER trial of the DSHNHL/GLA. J Clin Oncol. 2018;36(Suppl 15):S7574-7574.
35. Persky DO, Li H, Stephens DM, et al. Positron emission tomography-directed therapy for patients with limited-stage diffuse large B-cell lymphoma: results of Intergroup National Clinical Trials Network Study S1001. J Clin Oncol. 2020;38(26):3003-3011.
36. Freeman CL, Savage KJ, Villa DR, et al. Long-term results of PET-guided radiation in patients with advanced-stage diffuse large B-cell lymphoma treated with R-CHOP. Blood. 2021;137(7):929-938.
37. Phan J, Mazloom A, Medeiros LJ, et al. Benefit of consolidative radiation therapy in patients with diffuse large B-cell lymphoma treated with R-CHOP chemotherapy. J Clin Oncol. 2010;28(27):4170-4176.
38. Philip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. N Engl J Med. 1995;333(23):1540-1545.
39. Mundt AJ, Williams SF, Hallahan D. High dose chemotherapy and stem cell rescue for aggressive non-Hodgkin's lymphoma: pattern of failure and implications for involved-field radiotherapy. Int J Radiat Oncol Biol Phys. 1997;39(3):617-625.
40. Vose JM, Zhang MJ, Rowlings PA, et al. Autologous transplantation for diffuse aggressive non-Hodgkin's lymphoma in patients never achieving remission: a report from the Autologous Blood and Marrow Transplant Registry. J Clin Oncol. 2001;19(2):406-413.
41. Friedberg JW, Neuberg D, Monson E, Jallow H, Nadler LM, Freedman AS. The impact of external beam radiation therapy prior to autologous bone marrow transplantation in patients with non-Hodgkin's lymphoma. Biol Blood Marrow Transplant. 2001;7(8):446-453.
42. Hoppe BS, Moskowitz CH, Zhang Z, et al. The role of FDG-PET imaging and involved field radiotherapy in relapsed or refractory diffuse large B-cell lymphoma. Bone Marrow Transplant. 2009;43(12):941-948.
43. Biswas T, Dhakal S, Chen R, et al. Involved field radiation after autologous stem cell transplant for diffuse large B-cell lymphoma in the rituximab era. Int J Radiat Oncol Biol Phys. 2010;77(1):79-85.
44. Wendland MM, Smith DC, Boucher KM, et al. The impact of involved field radiation therapy in the treatment of relapsed or refractory non-Hodgkin lymphoma with high-dose chemotherapy followed by hematopoietic progenitor cell transplant. Am J Clin Oncol. 2007;30(2):156-162.
45. Wilke C, Cao Q, Dusenbery KE, et al. Role of consolidative radiation therapy after autologous hematopoietic cell transplantation for the treatment of relapsed or refractory Hodgkin lymphoma. Int J Radiat Oncol Biol Phys. 2017;99(1):94-102.
46. Yu Q, Zhang X, Wang N, et al. Radiation prior to chimeric antigen receptor T-cell therapy is an optimizing bridging strategy in relapsed/refractory aggressive B-cell lymphoma. Radiother Oncol. 2022;177:53-60.
47. Smith EL, Mailankody S, Staehr M, et al. BCMA-targeted CAR T-cell therapy plus radiotherapy for the treatment of refractory myeloma reveals potential synergy. Cancer Immunol Res. 2019;7(7):1047-1053.
48. Kostopoulos N, Bedgi S, Krimitza E, et al. Radiation therapy for bridging and improving CAR-T cell therapy. Int J Radiat Oncol Biol Phys. 2022;114(3):S83-S84.
49. DeSelm C, Palomba ML, Yahalom J, et al. Low-dose radiation conditioning Eenables CAR T cells to mitigate antigen escape. Mol Ther. 2018;26(11):2542-2552.
50. Breen WG, Hathcock MA, Young JR, et al. Metabolic characteristics and prognostic differentiation of aggressive lymphoma using one-month post-CAR-T FDG PET/CT. J Hematol Oncol. 2022;15(1):36.