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Early experience using salvage radiotherapy for relapsed/refractory non-Hodgkin lymphomas after CD19 CAR T-cell therapy

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Abstract

Radiotherapy is potentially an important salvage strategy post-chimeric antigen receptor T-cell therapy (CART) but limited data exist. We reviewed 14 patients treated with salvage radiation post-CART progression (SRT). Most received SRT for first post-CART relapse (71%) to sites

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previously PET-avid pre-CART (79%). Median overall survival (OS) post-SRT was 10m. Post-SRT, 6 localized relapses achieved 100% response (3=complete, 3=partial) with improved freedom from subsequent relapse (p=0.001) and OS (p=0.004) compared to advanced stage relapses. Three were bridged to allogeneic transplantation; at analysis, all were alive/NED. SRT has diverse utility and can integrate with novel agents or transplantation to attempt durable remissions.

Keywords

Chimeric antigen receptor T-cells; CART-cells; radiotherapy; salvage therapy; diffuse large B cell lymphoma; relapsed/refractory

Introduction:

Relapsed/refractory diffuse large B-cell lymphoma (DLBCL) remains a significant therapeutic challenge with poor outcomes (Crump et al, 2017). Anti-CD19 chimeric antigen receptor T-cell therapies (CART) (Sadelain et al, 2013) offer promise, with remarkable overall response rates (ORR) of 52-82% (Neelapu et al, 2017; Abramson et al, 2017; Schuster et al, 2019). However, sustained efficacy is limited with durable complete response (CR) rates of only ~40% (Nair & Neelapu, 2018). Overall survival (OS) for progressive disease (PD) post-CART is poor and significantly worse for early relapses (Chow et al, 2019). There is clear need to develop salvage strategies for this population, which is likely to grow rapidly with increased CART adoption and longer follow-up.

There is compelling rationale to consider salvage radiotherapy (SRT) for post-CART progression. SRT is effective for relapsed/refractory DLBCL as monotherapy and combined with systemic agents (Ng et al, 2018). Involved site RT before high dose therapy and autologous hematopoietic cell transplantation (HDT-AHCT) can improve outcomes (Hoppe et al, 2008). RT also has indirect immunomodulatory activity by converting irradiated cells into *in situ* vaccines, producing enhanced tumor-specific immunity against irradiated and distant sites (e.g., abscopal effect) (Buchwald et al, 2018). RT improves T-cell trafficking to irradiated sites, expands pre-existing T-cell clones and drives potential epitope spreading (Twyman-Saint Victor et al, 2015).

Limited data exist to guide optimal CART and RT integration. Our group demonstrated that low-dose RT conditioning can sensitize antigen negative tumor cells to CART-mediated elimination (DeSelm et al, 2018). While great attention has been focused on abscopal effects, this finding raises an alternative possibility that RT may instead mediate more efficient local cell killing, within irradiated sites. Despite strong scientific justification, there are no data describing SRT outcomes post-CART and we report our institutional early experience.

Materials and Methods:

Following IRB approval, we retrospectively analyzed 14 lymphoma patients (Table 1) who received SRT after CD19-directed CART at Memorial Sloan Kettering. All received photon SRT off-protocol and treatments were heterogeneous. The technique, doses and fractionation

were reflective of clinical urgency and multidisciplinary discussion. All were simulated for SRT using PET or CT based planning per standard institutional practice. Treatment volumes followed established involved site radiotherapy guidelines (Ng et al, 2018).

Overall response rate (ORR) was radiographic CR or partial response (PR) per Lugano criteria and presented as a proportion with an analyzable study at the relevant timepoint (Cheson et al, 2014). We define RD1 as first evidence of post-CART PD and RD2 as first evidence of post-SRT PD.

Kaplan-Meier survival analysis was performed from first date of SRT and differences between groups were assessed by log-rank. Patient outcomes were stratified by second-line age-adjusted International Prognostic Index (sAA-IPI) (Hamlin et al, 2003) determined pre-SRT. P-values of <0.05 were considered significant and statistics were performed using SPSS v26 (IBM).

Results

Patient and treatment characteristics

Cohort characteristics are detailed in Table 1. Patients were heavily pre-treated with median of 4 therapies pre-CART (range 2-8). Four (29%) had previous HDT-AHCT including 2 immediately pre-CART (Sauter et al, 2019). Patients received CART between 2014-2018. Four (29%) received commercial agents while 10 were treated per prospective protocols. Eight received JCAR017 (NCT02631044), 2 received our institutional anti-CD19 product, 19-28z, following AHCT (NCT01840566) and 1 received an EGFRt/19-28z/4-1BBL “armored” CART (NCT03085173).

Post-CART relapse

Median duration from CART to RD1 was 73d (range 26-367). Figure 1 shows a swimmer’s plot beginning at CART infusion (Day 0), with duration to RD1, SRT and post-SRT response. Three were primarily refractory to CART (2 biopsy confirmed); the remainder had at least PR on the first post-CART PET. Four (29%) received systemic therapy as their first post-CART treatment; ten (71%) had an RT-containing regimen.

Relapse patterns and SRT characteristics

At SRT, 8 (67%) had advanced stage relapse while 6 (43%) had localized recurrences. Two-thirds of patients and all localized recurrences were biopsied post-RD1 and all but 2 were concordant with initial diagnosis. Patient 14 had transformed FL pre-CART and relapsed with grade 3A FL with early transformation. Patient 11 was originally DLBCL, but relapsed with primary mediastinal B-cell lymphoma.

Post-CART pattern-of-failure analysis found that 11 (79%) relapsed in a previously PET-avid site including all low/low-intermediate risk recurrences (Supplemental Figure).

The main indication and dose of SRT is detailed in Figure 1A. Most advanced relapses were palliated with short, hypofractionated courses. Localized relapses were, in general, treated more definitively and typically received subsequent therapy. Five (33%) received SRT with

concurrent systemic therapies. Three with advanced disease continued systemic therapy post-SRT.

Most tolerated SRT well, but 3 (21%) terminated early. Patient 13 stopped after 18/20 planned fractions due to influenza. Patients 1 and 4 stopped SRT early given out-of-field PD. No unexpected, in-field toxicities attributable to SRT were noted.

Outcomes post SRT

Eleven had post-SRT radiographic restaging. This imaging was non-standardized and median duration from end of SRT to first restaging was 18d (range 1-252). ORR was 100% for the 6 localized relapses (n=3 CR, n=3 PR, Figure 1A). Advanced stage responses were more modest; while 5/7 had in-field PR, none had in-field or out-of-field CR with doses to 36 Gy, and most (71%) had concomitant out-of-field PD.

Median follow-up post-SRT was 10.2m (95%CI: 4.7-15.7) with median OS of 10.4m (95%CI: 0.4-20.3m). Median OS post-SRT was undefined and 2.6m (95%CI 2.1-3.0), for localized and advanced relapses, respectively. Compared to advanced stage relapses, localized relapses had significantly improved freedom from subsequent relapse (p=0.001) (Figure 1B) and OS (p=0.004) (Figure 1C). Though limited by small numbers, sAA-IPI was prognostic of OS post-SRT (p=0.006) (Figure 1D).

Eight relapses were recorded post-SRT. Five were out-of-field, and 3 were mixed in-and-out of field. Six patients received additional treatment for subsequent PD post-SRT.

SRT bridging to potentially curative treatments

Three with localized recurrences received SRT as a cytoreductive bridging strategy to alloHCT. They are alive/NED with 7.9, 9.8 and 38.8m of post-alloHCT follow-up, respectively. Patient 8 received SRT bridging to a second infusion of banked JCAR017 cells but progressed early and died 3m post-RD1.

Discussion

With two approved CART products and numerous others in development, we anticipate that the challenging clinical scenario of progression post-cellular therapy will become increasingly common. To our knowledge, this is the first report of SRT utilized post-CART. SRT has been adopted with two approaches, correlating with extent of disease at RD1. Patients with symptomatic, multifocal relapse received palliative RT in short courses. For localized disease, SRT was often utilized as part of a comprehensive strategy with effectively definitive intent. One patient with an indolent, localized relapse remains disease free at 2.5y post-SRT alone, highlighting the possibility of durable remissions.

We show early evidence that sAA-IPI may be prognostic post-CART similar to other relapsed/refractory settings (Hamlin et al, 2003), including post-alloHCT (Perales et al, 2010). One important reason why may be that the low/low-intermediate subgroups included the patients who underwent SRT bridging to alloHCT. Utilization of CART as a bridge to alloHCT has been proposed as a possible curative option, though principally studied for

acute lymphoblastic leukemia (Ghosh et al, 2017; Shalabi et al, 2018; Summers et al, 2018; Park et al, 2018). For lymphomas, positive pre-transplant PET is prognostic of relapse post-AHCT (Hoppe et al, 2009; Ulaner et al, 2015) and alloHCT (Bachanova et al, 2015). Peri-transplant RT can improve post-AHCT outcomes (Hoppe et al, 2008; Biswas et al, 2010; Coutu et al, 2015). Given that post-CART failures are likely chemoresistant, SRT may offer powerful cytoreduction. Increased numbers and longer follow-up is critical and this may be an important question for prospective research.

In our experience, post-CART relapses often involved sites of initially relapsed/refractory disease which recapitulates numerous DLBCL pattern-of-relapse studies, including post-AHCT(Hoppe et al, 2008, 2009; Biswas et al, 2010; Dhakal et al, 2016). While preliminary, our data suggest that the post-transplant relapse literature may offer lessons post-CART. For example, in a series of 100 patients with CR pre-AHCT, 40% with initially early stage and 76% with initially advanced stage relapsed in a previously-involved site (Dhakal et al, 2016). Of note, inclusion of RT significantly reduced this local failure. Consolidation RT either before or after CART to high-risk lesions (e.g., bulky, skeletal, extranodal, central nervous system) may thus be sensible.

An important justification for combining RT with CART is potential immune augmentation (Flynn et al, 2017; Honeychurch & Illidge, 2017). Preclinically, our group demonstrated that low-dose RT conditioning can sensitize antigen-negative tumor cells to CART-mediated elimination (DeSelm et al, 2018). This was achieved by activated CART secretion of TRAIL cytokines. TRAIL directed its effect via death receptors on proximal antigen-negative cells previously sensitized to this killing by the low-dose RT. Another potential mechanism of RT-CART synergy may be via abscopal effects, highlighted by a recent case report from our institution (Smith et al, 2019). Palliative radiotherapy delivered several days after B-cell maturation antigen (BCMA) CART infusion triggered robust T-cell repertoire expansion and cytokine-release syndrome-like symptoms in an advanced multiple myeloma patient. These effects, along with robust out-of-field radiographic response support an abscopal-like response (Smith et al, 2019). Despite steroids, there was BCMA CART persistence, raising the intriguing possibility that RT may influence both locally and distantly.

SRT fractionations used in this series varied but may be more similar to the low doses studied preclinically (DeSelm et al, 2018) over the higher doses per fraction typically felt to be required to trigger abscopal responses. However, optimal RT parameters necessary to elicit requisite immunogenicity for radiosensitive hematologic tumors is poorly defined. We did not observe any clear signs that SRT reinvigorated a dormant immune response outside of irradiated sites. However, this assessment was limited by the lack of pre- and post-SRT CART levels and correlatives.

We are currently studying potential benefits of radiotherapeutic conditioning pre-CART. Early data from Sloan Kettering (Imber et al, 2019) and others (Arscott et al, 2018; Sim et al, 2019) suggest that bridging RT is useful for palliation, cytoreduction and is associated with excellent CART ORR. Further inquiry is necessary to define how RT can be rationally integrated with other post-CART salvage options, including CART re-infusion, checkpoint blockade or targeted agents (Chow et al, 2019).

We acknowledge limitations including small sample, heterogeneous population and SRT regimens, and possible selection bias as only some were referred for SRT. Our ability to assess immunomodulation was challenged by the fact that responding patients had localized disease completely encompassed within SRT fields or soon underwent alloHSCT and the lack of translational correlatives.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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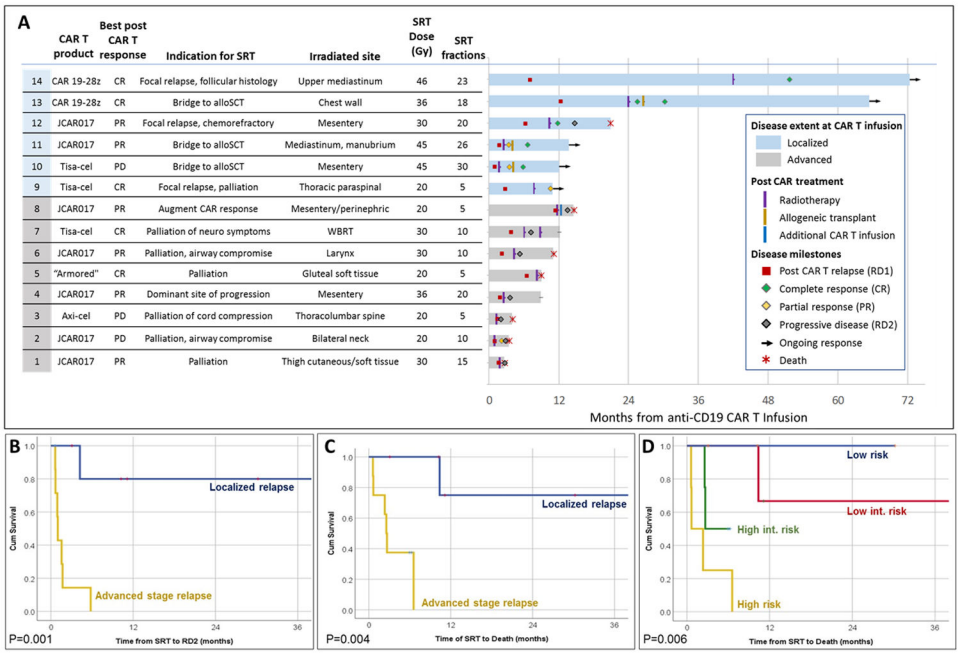

Figure 1.

A) Swimmer plot starting from Day 0 which is the date of CART infusion. Note that "Tisa-cel" refers to tisagenlecleucel, "Armored" refers to the EGFRt/19-28z/4-1BBL CART and "Axi-cel" is axicabtagene ciloleucel. B-D) Post SRT outcomes stratified by extent of relapsed disease. B) Freedom from subsequent relapse and C) OS. Of note, both outcomes calculated from the time of the first day of SRT. D) OS following SRT stratified by sAA-IPI at the time of SRT treatment.

Table 1.

Patient and treatment characteristics.

	n=14
Demographics	
Median age (range, years)	60 (24-78)
Male sex	12 (86%)
Histopathology	
DLBCL	12 (86%)
CD5+ high grade BCL	1 (7%)
Blastoid variant mantle cell	1 (7%)
DLBCL cell of origin (n=12)	
Germinal center B-cell	8 (67%)
Activated B-cell	4 (33%)
Transformed FL	4 (29%)
Pre-CART treatment history	
Median pre-CART regimens (range)	4 (2-8)
Pre-CART HDT+AHCT	4 (29%)
Prior radiotherapy	5 (36%)
CART treatment	
Product	
JCAR017	7 (50%)
Tisagenlecleucel (tisa-cel)	3 (21%)
19-28z	2 (14%)
Axicabtagene ciloleucel (axi-cel)	1 (7%)
EGFRt/19-28z/4-1BBL "armored" CAR	1 (7%)
Conditioning regimen	
Cyclophosphamide and fludarabine (Cy/Flu)	10 (71%)
Z-BEAM	1 (7%)
R-BEAM	1 (7%)
Bendamustine	1 (7%)
HiDAC + Dexamethasone + Cy/Flu	1 (7%)
Best post-CART response	
CR	5 (36%)
PR	6 (43%)
PD	3 (21%)
Median days to first post-CART relapse (range)	73 (26-367)
SRT characteristics	
Median duration from CART infusion to SRT (months)	5.3 (1.1-42.1)
RT given for first relapse	10 (71%)
Extent of disease at SRT	

	n=14
Localized	6 (43%)
Advanced	8 (67%)
sAA-IPI at SRT	
Low risk	3 (21%)
Low-intermediate risk	3 (21%)
High-intermediate risk	4 (29%)
High risk	4 (29%)
SRT treatment areas	
Extranodal	7 (50%)
Nodal	5 (36%)
Mixed nodal and extranodal	2 (14%)
SRT treatment modality	
Intensity modulated radiotherapy (IMRT)	7 (50%)
Conventional photon radiotherapy	5 (36%)
3D conformal radiotherapy	2 (14%)