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Adaptive bridging radiation therapy for relapsed/refractory B-cell lymphoma patient undergoing CAR T-cell therapy: Case report

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ABSTRACT

Radiation therapy (RT) is utilized as a bridging strategy for patients with aggressive B-cell lymphoma prior to CD19-targeted chimeric antigen receptor (CAR T)-cell therapy. RT has been shown to provide local control without exacerbating the toxicities associated with subsequent CAR T-cell infusion. However, a consensus on the optimal radiation dose and fractionation for bridging purposes has yet to be established. We present a case of a patient with relapsed aggressive B-cell lymphoma who underwent bridging adaptive RT on a CT-linac prior to receiving CAR T-cell therapy. At month 6 post-CAR T infusion, the patient demonstrates no signs of disease recurrence or relapse, nor any unexpected toxicities attributable to the combined treatment. This underscores the feasibility and success of this innovative approach in treating lymphoma patients undergoing CAR T-cell therapy.

Introduction

The landmark CD19-targeted chimeric antigen receptor (CAR T)-cell therapy trials have developed great promise for aggressive B-cell lymphoma patients who would otherwise have a dismal prognosis, leading to impressive overall response rates [1–3]. Patients with relapsed/refractory B-cell lymphoma who are eligible for CAR T-cell therapy often present with localized masses at a limited number of sites, which may either be symptomatic or become symptomatic during the 2–3 month period between the determination of eligibility and the infusion of CAR T-cell therapy [4]. Bridging therapy, whether it is systemic therapy, radiation therapy (RT), or both, given between apheresis and CAR T-cell infusion, plays a crucial role during this waiting period. RT is utilized as bridging therapy prior to CAR T-cell therapy, and it has been shown to be effective for local control without increasing the toxicities of subsequent CAR T infusion [4,5]. Though these studies have provided promising results with regards to using RT as a bridging approach in terms of toxicity profile and local antitumor effects, there is no established consensus for radiation dose/fractionation for the purposes of bridging RT.

Adaptive RT, based on CT-linac or MRI-linac technology, [6,7] makes it possible to modify the RT plan at each fraction based on real-time imaging to account for changes in tumor anatomy, to maximize tumor control and reduce normal tissue toxicity with real-time personalization of RT, using artificial intelligence (AI) under physician and physicist supervision. To our knowledge, while studies exist for solid tumors [8], there are no published studies to investigate adaptive RT in large B cell lymphomas. Therefore, we present a case of a patient with relapsed double-hit aggressive B-cell lymphoma who underwent bridging adaptive RT on a CT-linac prior to receiving CAR T-cell therapy. At month 6 post-CAR T infusion, the patient demonstrates no signs of disease recurrence or relapse, nor any unexpected toxicities attributable to the combined treatment.

Case presentation

A 57-year-old female presented with new onset left-sided back pain, with Computed tomography (CT) scan on Day −290 showing a large left retroperitoneal mass measuring 20 cm in diameter. The mass encased the aorta and invaded the left kidney, leading to obstructive hydronephrosis and a delayed nephrogram. Positron emission tomography/computed tomography (PET/CT) staging, performed on Day −274, demonstrated intensely avid disease within the left retroperitoneal region, thoracic and abdominal lymph nodes, and the peritoneum, associated with significant pain.

Histopathological analysis of a biopsy taken from the retroperitoneal

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mass on Day −280 confirmed the diagnosis of diffuse large B-cell lymphoma/high grade B-cell lymphoma, double expressor with MYC and BCL2 rearrangements (DLBCL/HGBCL-MYC/BCL2). The International Prognostic Index (IPI) score was determined to be 3, based on a lactate dehydrogenase (LDH) level of 857 U/L, extranodal site involvement, and a Stage IV disease classification. Treatment consisted of six cycles of dose-adjusted R-EPOCH and intrathecal methotrexate (IT MTX) for CNS prophylaxis, concluded on Day −157. Interim PET/CT after three cycles showed a markedly decreased uptake in prior FDG-avid disease (Deauville score of 5).

The end-of-treatment (EOT) PET/CT indicated an excellent response to treatment with near-complete resolution of all disease, albeit with some peripheral FDG avidity in the bulky retroperitoneal mass, likely reflective of inflammatory change or residual disease (Deauville score of 2). Consequently, a CT urogram and a repeat PET/CT in 6 weeks were recommended. Subsequent PET scanning on Day −77 revealed stable uptake in the left retroperitoneal mass with central photopenia.

Of note, a new focus of intense FDG avidity was observed within the umbilicus (SUVmax: 5.5), corresponding to a 4 mm soft tissue nodule, deemed indeterminate. On examination during radiation oncology consultation, a 1 cm area of firmness at the umbilicus was noted. The rationale for consolidative RT to the area of bulky disease was thoroughly discussed, with the distinction between residual lymphoma and inflammation remaining uncertain without biopsy. A short-interval repeat PET/CT scan was recommended to evaluate uptake in the site of bulky disease and the umbilicus.

Her repeat PET/CT on Day −41 demonstrated stable peripheral FDG avidity in the bulky retroperitoneal mass persisted (SUVmax: 3.1), alongside increased uptake in the umbilical soft tissue nodule, measuring up to 1.8 cm. An expeditious IR biopsy was planned to evaluate for relapsed disease. Following the confirmation of lymphoma recurrence in the umbilical lesion on Day −28, CAR-T therapy was recommended, and the patient was planned for bridging RT prior to initiating CAR-T. Subsequently, apheresis was performed on Day −21.

Bridging RT was recommended for both the umbilical and retroperitoneal soft tissue masses in preparation for CAR-T therapy. After obtaining patient consent, she elected to proceed with the administration of Ethos adaptive radiation therapy to modify the radiation field, considering the radiosensitivity of lymphoma. This involved delivering one fraction of 5 Gy once weekly, up to a maximum of 25 Gy in total, depending on the patient's response and the timing of CAR-T therapy. In addition, given that her left pelvic mass was immediately adjacent to her left kidney, adaptive RT would be an ideal asset to optimally spare any functional kidney tissue from the RT dose.

4D CT scan was acquired. ITV was contoured on MIP (mean intensity projection) CT and rechecked on 10 respiratory phases. There was a 0 mm PTV margin. Patient was planned with intensity-modulated radiation therapy (IMRT) using 9 equidistant fields. On Day −11, the patient

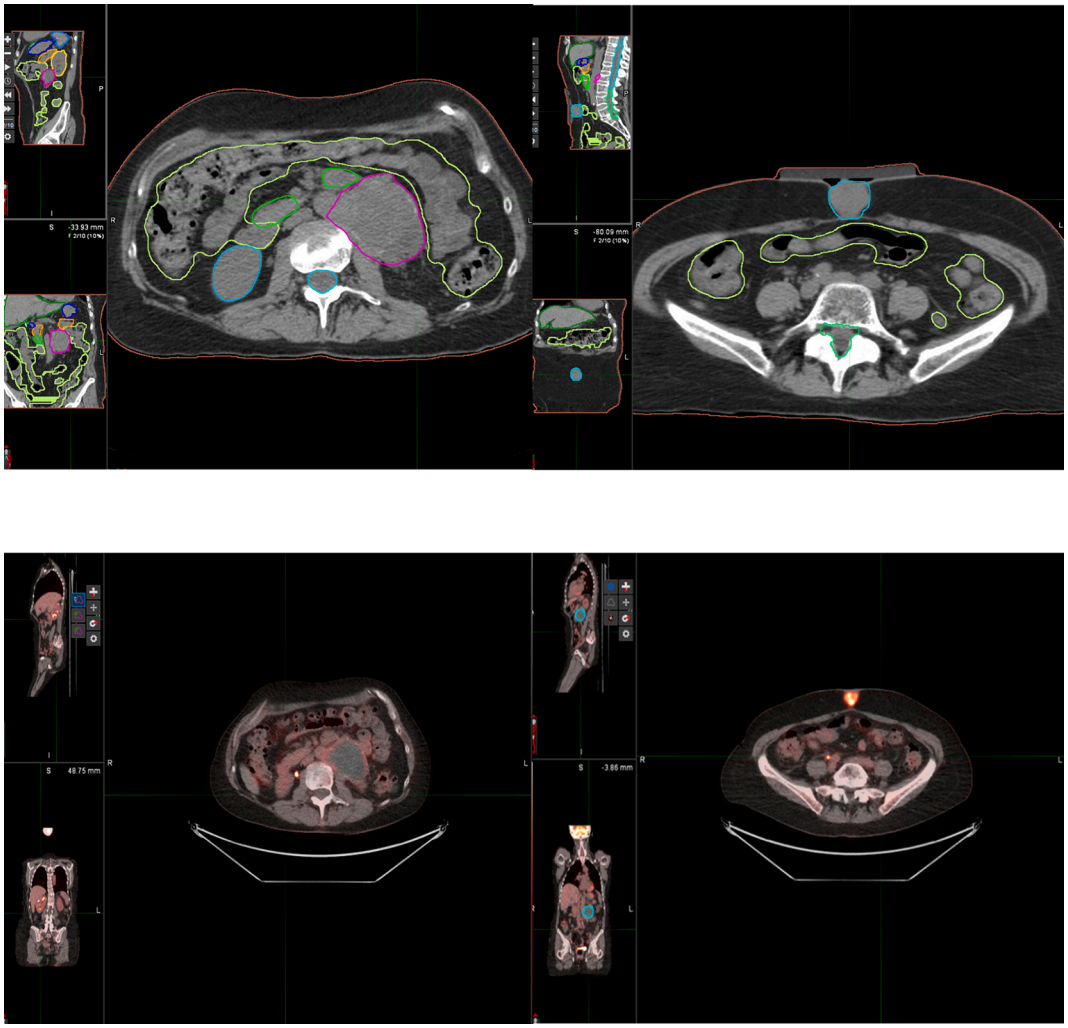

Fig. 1. (A-D): Pre-adaptive RT CT simulation scans and post-adaptive RT PET/CT scans, demonstrating the tumor response to online adaptive RT before CAR T-cell therapy infusion. (A) Retroperitoneal mass, CT simulation scan pre-adaptive RT; (B) Umbilical mass, CT simulation scan pre-adaptive RT; (C) Retroperitoneal mass, post-adaptive RT PET/CT scan; (D) Umbilical mass, post-adaptive RT PET/CT scan.

responded well after the first fraction of RT (5 Gy), experiencing only some self-resolving nausea without any other complications. By the time of the second fraction, a reduction in the size of the *peri*-umbilical tumor was noted by the patient, accompanied by resolution of pain in this area. Tumor response was evaluated using Ethos imaging, which confirmed interval tumor shrinkage in both the retroperitoneal and umbilical masses. As such, additional RT was not administered as the CAR T cells were prepared for infusion sooner than anticipated. Consequently, the patient proceeded with CAR T-cell therapy. An interim PET/CT scan post-RT pre-CAR T was conducted on Day −7, showing the response to adaptive RT. The volume of retroperitoneal mass reduced from 226.14 cm^3 to 131.14 cm^3, and the volume of umbilical mass decreased from 71.7 cm^3 to 14.47 cm^3. Fig. 1 (A-D).

On Day 0, the patient was administered axicabtagene ciloleucel (Axicel) CAR T-cells, following outpatient lymphodepleting chemotherapy with fludarabine and cyclophosphamide, which was well-tolerated without any incidents. The infusion of CAR-T cells, dosed at 2x10^6 cells per kilogram for a total volume of 68 ml, was performed without any adverse events, and the patient's vital signs remained stable throughout the procedure.

Subsequently, the patient developed grade 1 cytokine release syndrome (CRS) with a maximum temperature (Tmax) of 103.7°F. Treatment included tocilizumab on Day + 1 and Day + 2 and dexamethasone (10 mg intravenously) on Day + 1. Subsequently, the patient developed Grade 3 immune effector cell-associated neurotoxicity syndrome (ICANS), with an ICE (Immune effector Cell-associated Encephalopathy) score of 1/10, prompting the administration of dexamethasone (10 mg IV) and the initiation of standing anakinra treatment. Given elevated interleukin-6 (IL-6) levels, exceeding 1000, siltuximab was also given, resulting in notable improvement. Steroid therapy was gradually tapered and discontinued by Day + 9, with anakinra cessation on Day + 10. The patient achieved full recovery from both grade 1 CRS and grade 3 ICANS, leading to her discharge on Day + 11.

Her EOT scan conducted on Day 30 post CAR T, demonstrated a very good partial response (Deauville score of 5). Residual avidity was observed, which may be attributed to residual disease, CAR T-related inflammation, or healing from a superinfection. Laboratory studies conducted around this time revealed normal renal and liver chemistries, a normal LDH level, and modest cytopenias that required no intervention. Given that responses can continue to deepen over time, a plan was made to repeat the PET/CT scan in one month to assess the evolution of the response.

The repeat PET/CT scan on Day 60 post-CAR T showed an improving response. The scan was classified as a Deauville 3 response, consistent with a complete metabolic response. Laboratory studies conducted concurrently noted normal renal and liver chemistries, a normal LDH, and modest cytopenias, again requiring no intervention. CT scans done at month 3 and month 6 post-CAR T demonstrated no evidence of recurrent disease.

Discussion

This case represents the successful application of adaptive RT in patients with lymphoma undergoing CAR T-cell therapy. The PET/CT conducted following RT and before CAR T infusion revealed significant disease regression, consistent with a partial response. The patient then successfully underwent LDC and CAR T infusion after adaptive bridging RT. Furthermore, in this particular case, we were able to comprehensively treat two sites of disease with excellent responses. This supports the growing body of literature indicating that comprehensive RT typically yields more favorable outcomes compared to focal RT [5,9]. It's important to note, however, that comprehensive RT is generally applied in clinical practice to patients with a limited number of disease sites [4]. However, recent evidence suggests that treating up to five lesions comprehensively in the bridging setting can lead to better patient outcomes [10]. Additionally, when considering adaptive RT, we must acknowledge the practical limitations due to time constraints in treating multiple lesions. Therefore, this approach warrants further investigation to optimize its application and effectiveness in various clinical scenarios.

Utilizing Ethos CBCT, this technique personalizes the number of fractions, total dose of RT, and volume of the irradiated field for each fraction. By personalizing the RT dose and volume based on tumor response using Ethos adaptive therapy and allowing a week between fractions for tumor response to be visualized in real-time, patients are less likely to have RT-induced toxicities by the time they are about to undergo CAR T-cell therapy. During each adaptive treatment, the target volume is re-contoured and evaluated by the attending radiation oncologist, who then optimizes a new treatment plan based on the current day's anatomy. CBCT facilitates decision-making by assessing the response and determining whether the patient should receive additional RT based on predefined criteria for up to five fractions. While one might argue that this duration could be longer than conventional daily fractionated RT, the radiosensitivity of lymphoma to RT leads us to expect that the majority of patients will receive less than the planned sessions before proceeding to CAR T-cell therapy. Therefore, we are conducting a pilot trial to investigate once-weekly RT using AI-driven adaptive RT technology to optimize bridging RT dose and field in terms of logistics, time, cost, and toxicities of RT (open to accrual, clinicaltrials.gov, NCT06004167). Currently, several clinical trials are also underway to explore the optimal RT dose/fractionation scheme, as well as the dose–response relationship and RT field size (NCT06004167, NCT05514327, NCT05621096, NCT05621096, NCT05574114, and NCT05800405), with the expectation of yielding valuable insights in the near future.

Author Contributions

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

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [H.S.A: None. PCJ: reports a consultancy role for Bristol Myers Squibb, Abbvie, ADC Therapeutics, AstraZeneca, Incyte, and Seagen; research funding from Medically Home, and Incyte, JP: None, C.G.P: reports research grant from Varian].

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