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Teaching Case

Role of Radiation in Combination With CD30-Directed Chimeric Antigen Receptor T-Cell Therapy for Relapsed/Refractory Hodgkin Lymphoma

Colton Ladbury, MD,[a,1] Claire Hao, BS,[a,1] Matthew Mei, MD,[b] Alex Herrera, MD,[b] Garth Green, MD,[a] and Savita Dandapani, MD, PhD[a,*]

[a]*Department of Radiation Oncology, City of Hope National Medical Center, Duarte, California; and* [b]*Department of Hematology & Hematopoietic Cell Transplantation, City of Hope National Medical Center, Duarte, California*

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Introduction

The prognosis of patients with relapsed/refractory Hodgkin Lymphoma (R/R HL) has improved over the years, but effective therapies for multiply relapsed disease, including in patients refractory to brentuximab vedotin and programmed cell death-1 blockade remain an unmet need. CD30-directed chimeric antigen receptor (CAR) T-cell therapy is an investigational treatment option for patients with R/R HL that has demonstrated favorable tolerability and clinical efficacy in phase 1/2 trials, with 1-year progression-free survival and overall survival (OS) of 36% and 94%, respectively.[1-3]

In R/R large B-cell lymphoma treated with CAR T-cell therapy, both bridging (bRT)[4-8] and salvage[8,9] radiation therapy (RT) having been shown to be effective. However, as CAR T-cell therapy for R/R HL remains experimental at this time, there is a paucity of literature regarding the role of radiation therapy in combination with CD30-directed CAR T-cell therapy for R/R HL. HL is known to be sensitive to radiation,[10] and considering the potential synergy between bRT and CAR T-cell therapy in large B-cell lymphoma, it is logical to explore the role of peri-CAR T-cell RT.

In the bridging setting, RT could add value by decreasing tumor burden, as pretherapy metabolic tumor volume is associated with response to CAR T-cell therapy.[11] It is also thought to provide an immunostimulatory effect that could potentiate the efficacy of the CAR T-cell therapy. In the salvage setting, radiation has led to favorable responses in a fraction of patients who relapse with limited disease after autologous transplant.[12] Here we present 2 patients with R/R HL who underwent infusion of CD30-directed CAR T-cell therapy (given as part of a prospective trial; NCT04268706), one of whom received bridging and salvage radiation and another whom received salvage radiation.

Case 1

A 19-year-old man (Eastern Cooperative Oncology Group [ECOG] Performance Status 0) was initially diagnosed with nonbulky stage I mixed-cellularity classical HL (CD15+, CD30+, CD20-, CD3-, CD45-) after workup of right cervical lymphadenopathy that did not respond to antibiotics. At that time, computed tomography (CT) showed numerous enlarged lymph nodes in the right neck with the largest measuring 4.5 × 3.9 cm. His initial treatment course consisted of 3 cycles of doxorubicin,

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[1]C.L. and C.H. contributed equally to this work.

*Corresponding author: Savita Dandapani, MD, PhD; Email: sdandapani@coh.org

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bleomycin sulfate, vinblastine sulfate, and dacarbazine (ABVD). Subsequent CT showed persistent bulky disease in the right cervical and supraclavicular regions as well as the bilateral axillae.

During the next 2 years he underwent a multitude (8 lines of treatment) of salvage therapies. Although some of these therapies yielded transient responses, he continued to have progressive disease and was ultimately evaluated for CD30-directed CAR T-cell therapy.

At the time of initial referral to radiation oncology department, positron emission tomography (PET) showed bulky disease in the right cervical, axillary, retropectoral, and anterior mediastinal nodal regions. The right neck disease was associated with significant pain. After leukapheresis he was recommended bridging radiation to the right neck as a means of treating symptomatic disease and in the hope of a synergistic immune-stimulatory effect. The region of interest measured 15 × 10 cm with a maximum standardized uptake value (SUV_{max}) of 23.6 g/mL (Fig. 1A). He was treated to a total dose of 20 Gy in 10 fractions using an anteroposterior-posteroanterior (AP/PA) technique. Only gross tumor was targeted in the gross tumor volume (GTV; Fig. 2) with no clinical target volume (CTV). Comprehensive radiation was not used because of the limitations of the Institutional Review Board protocol, which required that there be PET avid disease at the time of CAR T-cell infusion. Radiation was well tolerated with no acute toxicities. On the pre-CAR T-cell PET/CT, the treated region decreased to 10.9 × 6.9 cm with an SUV_{max} of 4.4 g/mL (Fig. 1B) and he had improvement in discomfort though he still had symptoms from his untreated sites.

Approximately 1 month after completion of radiation he underwent lymphodepletion with fludarabine and bendamustine followed by CAR T-cell infusion. A PET/CT obtained a month and a half after infusion showed stable disease overall. The irradiated lesion now measured 10.8 × 6.9 cm with an SUV_{max} of 8.65 g/mL (Fig. 1C). He was then offered salvage radiation therapy to bulky sites, including most of the disease in the right neck, chest wall, and axilla. He was treated to a total dose of 38 Gy in 19 fractions using a helical tomotherapy intensity modulated radiation therapy technique to respect spinal cord and brachial plexus organs at risk. Again, that target primarily included only GTV, though a limited CTV in adjacent elective nodal regions was included. He tolerated treatment well, with grade 2 mucositis and grade 1 dermatitis, dry mouth, and dysgeusia.

His next PET/CT 3 months later showed near complete remission with near resolution of associated symptoms (Fig. 1D). Therefore, he underwent consolidation with 2 cycles of gemcitabine, vinorelbine, doxorubicin followed by allogeneic transplant (matched sibling donor) with fludarabine, cyclophosphamide, and total body irradiation conditioning (2 Gy in 1 fraction), and posttransplant cyclophosphamide, tacrolimus, and mycophenalate mofetil for graft-versus-host disease prophylaxis. Unfortunately, 3 months after allogeneic transplant he again relapsed in the right neck (in-field) and mediastinum (Fig. 1E). Subsequent salvage therapies included

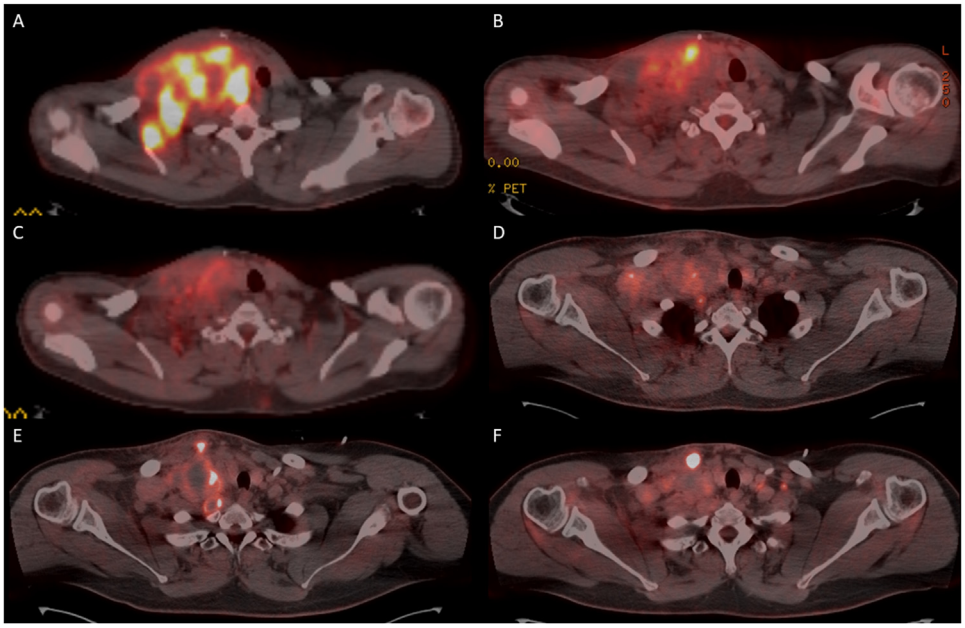

Figure 1 Fluorodeoxyglucose positron emission tomography/computed tomography for case 1. (A) Before bridging radiation therapy. (B) After bridging radiation therapy before Chimeric antigen receptor T-cell infusion and (C) 1-month post Chimeric antigen receptor T-cell infusion. (D) After salvage radiation therapy. (E) Relapse after radiation therapy. (F) At last follow-up.

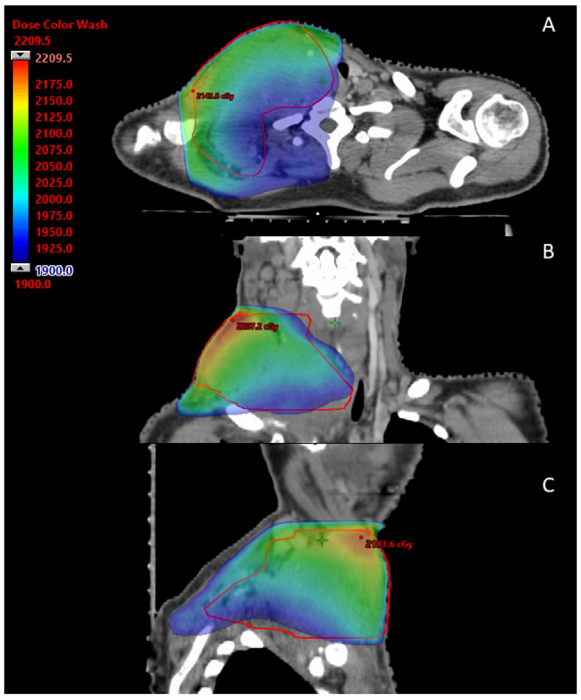

Figure 2 Bridging radiation treatment volumes and plan for case 1, in the (A) axial, (B) coronal, and (C) sagittal views, with the treated gross tumor volume outlined in red. Dose wash shows the 95% isodose line and higher.

nivolumab, nivolumab with decitabine, and BV. He also received additional salvage radiation to the right neck to a total dose of 4 Gy in 2 fractions using an AP/PA technique, concurrent with nivolumab and BV. Although there was an initial partial response, the most recent PET/CT a year and a half after CAR T-cell therapy demonstrates progression in the bilateral cervical nodes (in-field), right axilla, and anterior mediastinum (Fig. 1F). At last follow-up, he was continuing on nivolumab and BV while awaiting additional clinical trial options.

Case 2

A 29-year-old woman was initially diagnosed with stage IIIB classical HL after presenting with fever, chills, night sweats, and weight loss. Initial therapy consisted of 6 cycles of doxorubicin, bleomycin sulfate, vinblastine sulfate, and dacarbazine. Follow-up PET/CT showed disease progression in the bilateral cervical, left supraclavicular, mediastinal, and retroperitoneal lymph node regions. She underwent 5 subsequent lines of therapy but ultimately continued to progress (Fig. 3A). She was therefore evaluated for CD30-directed CAR T-cell therapy on an Institutional Review Board-approved protocol.

Approximately 2 and a half months after leukapheresis, she underwent lymphodepletion with fludarabine and bendamustine followed by CAR T-cell infusion, and PET/CT scans performed 6 and 12 weeks after infusion demonstrated complete response (Fig. 3B). Six months after infusion, recurrence in a right retropectoral lymph node was noted, which measured 3.3 × 1.7 cm with an SUV_{max} of 12.88 g/mL for which she was referred for salvage radiation therapy (Fig. 3C). The scan did also show a nodular density in the left external iliac region measuring 1.7 × 1.2 cm with an SUV_{max} of 4.72 g/mL that was new but of unclear cause.

She received salvage radiation to the right axillary and supraclavicular region to a total dose of 40 Gy in 20 fractions using an AP/PA technique. The radiation volumes were designed to treat the GTV as well as the nearby elective nodal volume as a CTV (Fig. 4). She tolerated treatment well, with grade 1 radiation dermatitis and no other toxicity.

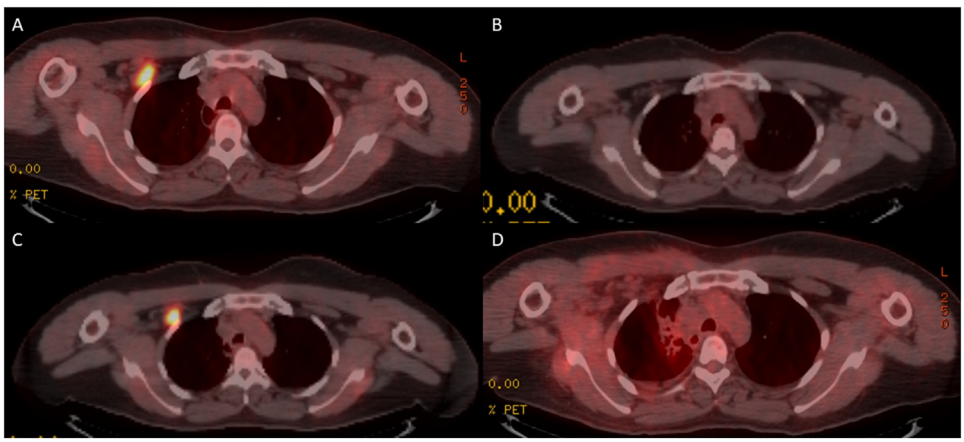

Figure 3 Fluorodeoxyglucose positron emission tomography/computed tomography for case 2 (A) Before Chimeric antigen receptor (CAR)-T cell infusion and (B) 1-month post-CAR T-cell infusion. (C) Relapse post-CAR T-cell therapy. (D) After salvage radiation therapy.

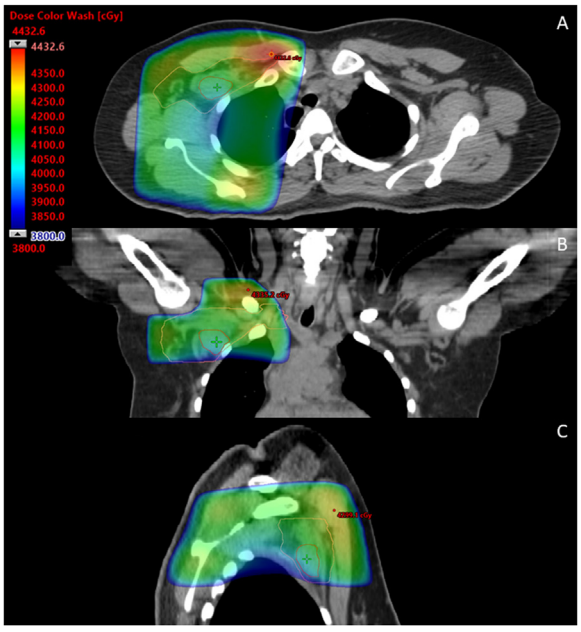

Figure 4 Radiation treatment volumes and plan for case 2, in the (A) axial, (B) coronal, and (C) sagittal views, with the gross tumor volume outlined in red and the clinical target volume outlined in coral. Dose wash shows the 95% isodose line and higher.

Follow-up PET/CT 3 months later showed complete response (Fig. 3D). Six months later, however, she had progression in the previously noted left anterior external iliac node. Of note, the left axillary region remained controlled. The external iliac node measured 2.8 × 2.2 cm with an SUV_{max} of 11.5 g/mL. As of last follow-up a year and 3 months after CAR T-cell infusion, the left external iliac region remains her only site of disease and she is currently undergoing treatment on a separate clinical trial.

Discussion

Although still experimental, CD30-directed CAR T-cell therapy for R/R HL is a promising treatment option that has been shown to be both safe and effective in early clinical trials. In a seminal publication on 2 parallel phase 1/2 trials, CD30 CAR T-cell infusion was administered after fludarabine-based lymphodepletion in 32 patients.[1] The overall response rate was 72%, with 59% of patients experiencing complete responses. This led to 1-year progression-free survival and OS rates of 36% and 94%, respectively. Although these results are promising compared with historical options for R/R HL, there is room for improvement. On this trial, 67% of patients received bridging chemotherapy. All 4 patients who achieved a complete response to bridging therapy maintained a complete response at their first disease assessment, and 2 patients remain without progression at last follow-up. This highlights the potential value of using bridging therapy to debulk tumors before CAR T-cell infusion. Although no patients received bRT, it is an attractive option because of the high radiosensitivity of HL.[10] Furthermore, because pretherapy metabolic tumor volume was associated with response to CAR T-cell therapy,[11] using radiation to cytoreduce gross disease could facilitate improved outcomes. Similarly, for patients who relapse after CAR T-cell therapy, salvage radiation may provide benefit by effectively controlling targeted gross disease.

To our knowledge, there is no literature on the use of bridging or salvage radiation combined with CAR T-cell therapy for HL. However, several studies have been published in NHL.[4-9] Studies on bridging therapy suggest that bridging radiation is well-tolerated and can yield favorable responses, particularly if all metabolic disease can be incorporated into the radiation field. In the largest study assessing this by Pinnix et al, 9 patients who received comprehensive radiation to all metabolic disease achieved improved outcomes compared with 8 patients who only received focal radiation.[6] However, significant selection bias no doubt contributes to the favorable outcomes observed, as patients with higher disease burden are less likely to be eligible for comprehensive radiation. The patient in our case series who received bridging radiation was unable to receive comprehensive bRT due to a protocol requirement that active disease be present immediately before CAR T-cell therapy. Nonetheless, bRT provided symptomatic relief and resulted in a near complete response in that area. Ideally, the benefits of comprehensive bridging therapy on R/R HL patients with more limited disease burden will be thoroughly examined in the future to determine whether they mirror results in NHL.

However, the rationale behind bridging and salvage radiation may not necessitate treating all disease. Rather, radiation is used as a local therapy for symptomatic or bulky disease and may aid in control of particularly troublesome sites. The value of radiation as a debulking therapy may be even greater than what is seen in NHL because HL tends to spread more contiguously.[13] There is also evidence that radiation can help with cytoreduction, lymphodepletion, treatment of sanctuary sites, and enhancement of the immune response.[14,15] In total, radiation administered either before or after CAR T-cell infusion may act synergistically with systemic treatments that can address microscopic disease, ultimately improving the patient response.

Identification of a suitable dose is also critical. In our case, 20 Gy in 10 fractions was insufficient for bulky disease, although based off experiences in NHL, it may be sufficient for less bulky disease.[4-9] In NHL, preliminary data suggest that achieving a dose of at least 37.5 Gy or an equivalent dose in 2 Gy fractions of 39.5 Gy may be associated with reduced failures, although a median dose of 24 Gy resulted in low local failure rates.[16] Furthermore, 77% of local failures occurred in lesions >50 cc. Thus, one

might choose dosing based off risk factors, which have been shown to include lesion size and SUV.[17] Under such a paradigm, high-risk lesions could receive higher doses while lower risk lesions could receive lower doses, which optimally would enable a more effective comprehensive treatment without excessive toxicity. Such an approach is used in our trial of bridging radiation therapy for NHL (NCT05800405).

Less research has been done on salvage radiation therapy (SRT) after CAR T-cell therapy, even in NHL. The largest series was done by Imber et al,[9] who evaluated 14 NHL patients treated with salvage radiation. Six patients had localized relapses while 8 had more advanced relapses. Median OS post-SRT was 10 months. In patients with limited relapse, both freedom from subsequent relapse ($P = .001$) and OS ($P = .004$) were significantly improved. Therefore, it is unsurprising that the patient in case 1 progressed after his first course of salvage radiation as he had advanced and bulky disease. In contrast, the patient in case 2 was thought to have localized disease but progressed at an untreated site that was identified retrospectively, although the treated subpectoral site was controlled. This could be a testament to the potential value of a combined approach, where radiation can target gross disease while systemic therapies can address microscopic areas of relapse before they become clinically appreciable. This approach may also be beneficial because patients who have relapsed after CAR T-cell infusion are typically heavily pretreated with highly refractory disease. Additional evaluation of salvage strategies will be required to determine optimal sequencing and combinations.

Conclusion

The role of CAR T-cell therapy in the management of R/R HL continues to be evaluated. In these patients, it will be important to characterize what other treatment modalities might synergize as either bridging or salvage therapies. This is the first report of bridging and salvage radiation in the setting of CD30-directed CAR T-cell therapy for R/R HL. The highly radiosensitive nature of HL may be leveraged by using radiation to debulk tumors in the bridging period before CAR T-cell infusion or to control limited relapses in the salvage setting after CAR T-cell infusion. These approaches have appeared effective in NHL and warrant further investigation concurrent with advances in cellular therapy in R/R HL.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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