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Proton Therapy as a Bridging Treatment in CAR T-Cell Therapy for Relapsed and Refractory Large B-Cell Lymphoma: Is There a Role?

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Abstract

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma. Since the relapse rate of DLBCL to frontline chemoimmunotherapy and salvage autologous hematopoietic cell transplant is high, CD19-directed chimeric antigen receptor (CAR) T-cell therapy was adopted. Given the time interval needed for CAR T cells to be manufactured (3-5 weeks) and the aggressiveness of these relapsed/refractory lymphomas, some patients do not make it to the CAR T-cell infusion phase. This calls for a bridging therapy to control, debulk, and sensitize the disease during this period. Radiation therapy can serve this purpose and has shown promising results in some studies. Proton therapy, compared to standard radiation therapy, in some locations, can reduce the radiation dose to the organs at risk, which may lead to fewer side effects for patients with lymphomas. Thus, we hypothesize that proton therapy may serve as a promising bridging strategy to CAR T-cell therapy for some patients.

Keywords: CAR T-cell therapy; proton therapy; bridging therapy; non-Hodgkin lymphoma

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Introduction

Non-Hodgkin lymphoma is the most common hematologic malignancy [1]. It accounts for 4.3% of all cancers in the United States, ranked as the seventh most common cancer among males and the sixth among females [2]. Among all non-Hodgkin lymphoma subtypes, diffuse large B-cell lymphoma (DLBCL) is the most common, accounting for 30% to 40% of all cases [3]. Main frontline treatment for DLBCL includes chemo-immunotherapy with/without radiation therapy. Up to 90% of patients achieve an objective response after frontline treatment with anthracycline-based chemoimmunotherapy combining cyclophosphamide, vincristine, doxorubicin, and prednisone and the anti-CD20 monoclonal antibody rituximab (R-CHOP); of these 10% to 30% will relapse [4, 5]. The standard salvage therapy includes second-line chemotherapy followed by high-dose chemotherapy and autologous hematopoietic cell transplant (auto-HCT) [6], with relapse rates of approximately 20% to 50% or higher in patients with complete metabolic

response versus those attaining a partial metabolic response or less as assessed by positron emission tomography–computed tomography to second-line chemotherapy [7].

No standard therapy exists for patients who have relapse following auto-HCT or after failure of 2 or more lines of therapies in transplant-ineligible cases [8]. Depending on a number of factors, patients may receive third-line chemotherapy, targeted therapy, allogeneic HCT, and most recently CD19-directed chimeric antigen receptor (CAR) T-cell therapy, which have demonstrated objective response rate of 52% to 82%, and complete remission of 40% to 52% [9–11].

Radiation therapy has also been an effective treatment of DLBCL during the past century. Initially it was viewed as a palliative treatment modality for DLBCL, then later as a potentially curative treatment before the widespread use of chemotherapy. Currently it plays important roles in consolidation of first-line therapy and peritransplant treatments [4, 12, 13]. Recently, radiation has been considered as a bridging strategy to CAR T-cell therapy to debulk tumor burden, preserve performance status, and achieve the needed lymphodepletion until the CAR T cells are manufactured and ready to be infused [14, 15]. Multiple forms of radiation therapy are commonly used to treat lymphoma, including electrons, photons, and protons. Of these, proton therapy has the greatest potential to reduce collateral radiation to uninvolved organs [16]. In this review, we provide an overview of CAR T-cell therapy in relapsed DLBCL and discuss the possible role of proton therapy as a bridging tool for CAR T-cell therapy.

Role of CAR T-Cell Therapy in the Treatment of Relapsed DLBCL

Currently, CAR T-cell therapy is indicated for large B-cell lymphoma that fails 2 or more lines of therapies. CAR T-cell therapy is an autologous cellular immunotherapy that uses the patient's own T lymphocytes and genetically reengineers them to recognize and attack cancerous cells. CD19 glycoprotein is uniformly expressed in all stages of B-cell maturation and is expressed in more than 95% of B-cell malignancies [17], which makes it an ideal target for CAR T cells to recognize. CAR T cells have additional activation and recognition domains that allow them to expand and proliferate [18]. First-generation CAR T cells showed limited antitumor activity owing to weak proliferation and persistence [19]. Consequently, costimulatory domains were added to second-generation CAR T cells, which significantly improved proliferation, persistence, and signaling strength [20]. The most commonly used costimulatory domains are CD28 and 41BB.

The CAR T-cell manufacturing process starts with leukapheresis, the harvesting of the patient's own lymphocytes. Subsequently, T cells are transfected with a replication-defective virus (lentivirus or retrovirus) that holds the *CAR* gene. CAR T cells are then expanded in vitro and infused back to the patient approximately 3 weeks later [21, 22]. A lymphodepleting chemotherapy regimen is commonly prescribed a few days before infusing the CAR T cells to facilitate homeostatic cell proliferation. Fludarabine and cyclophosphamide chemotherapy is the most commonly prescribed combination therapy for such purpose [23]; however, the JULIET study also allowed bendamustine for 2 days [10]. Regrettably, one of the main issues with this treatment approach is the length of time to infusion of the CAR T-cell therapy, which provides time for the DLBCL to progress; as a result, in the ZUMA-1 trial, approximately 10% of patients did not end up receiving the CAR-T product [11]. Therefore, different treatment approaches have been developed to try to control the lymphoma during the manufacturing phase, or provide a "bridging treatment" until the CAR T-cell infusion.

The 2 CAR T-cell therapies that are US Food and Drug Administration approved for the treatment of relapsed and/or refractory (R/R) large B-cell lymphoma are axicabtagene ciloleucel (axi-cel) and tisagenlecleucel (tisa-cel), which have CD28 and CD41BB as costimulatory domains, respectively. Axi-cel proved effective for the treatment of R/R large B-cell lymphoma in the ZUMA-1 trial, showing a 1-year objective response rate and complete remission of 82% and 54%, respectively, and progression-free survival of 41% at 15 months. No bridging therapy was allowed, and lymphodepletion followed a 3-day course of fludarabine and cyclophosphamide [9, 24]. Similarly, tisa-cel proved effective in the JULIET trial, achieving a best overall response rate of 52% and 1-year relapse-free survival rate of 65%. Ninety percent of patients in this trial received bridging therapy (54% received rituximab, and 40% received gemcitabine), and 93% received lymphodepleting chemotherapy with either fludarabine and cyclophosphamide, or bendamustine [10].

CAR T-cell therapy brings a new array of toxicities, and several studies have described these side effects [25, 26]. To date, the most concerning are cytokine release syndrome (CRS) and neurotoxicity. Depending on the prescribed product, incidence of CRS ranges from 50% to 93% [10, 11, 27] and is purportedly due to the excessive release of cytokines as CAR T cells expand, proliferate, and attack lymphoma cells. This might be more prominent in the presence of bulky and extensive disease as seen with high leukemia burden [28, 29]. The incidence of neurotoxicity also varies depending on the prescribed product, with reported incidence (any grade) of approximately 20% with tisa-cel and up to 64% with axi-cel [10, 11] and is thought to

result from the ability of the CAR T cells to cross the blood-brain barrier, causing inflammation in the central nervous system. Although CRS can be managed with tociluzumab (anti–interleukin 6 receptor) and siltuximab (anti–interleukin 6 antibody), it is critical enough and may require admission and observation in the intensive care unit in the presence of serious compromise of organ function. Neurotoxicity is generally treated with corticosteroids; however, high-grade neurotoxicity may require aggressive interventions, including airway protection [30].

Role of Radiation Therapy in the Treatment of DLBCL

Radiation therapy is an effective treatment for DLBCL as consolidation treatment following chemotherapy in early stage [31] and for patients with bulky disease [32, 33]. Moreover, radiation plays a role in achieving local control in some cases with relapsed DLBCL that become refractory to chemotherapy and stem cell transplant [4, 12, 34, 35]. On the other hand, radiation therapy for lymphoma can have acute and long-term toxicities. While acute toxicities are generally mild and can include hematologic suppression, dermatitis, mucositis, esophagitis, nausea, diarrhea, fatigue, and/or constipation, the late effects can be more significant and include cardiac toxicity, pulmonary fibrosis, and second malignancies. New strategies have been developed to reduce radiation toxicity, including decreasing the radiation dose and field size, using modern radiation therapy techniques, such as intensity-modulated radiation therapy (IMRT), and using proton therapy. International Lymphoma Radiation Oncology Group (ILROG) developed standard involved site radiation therapy guidelines for nodal and extranodal lymphomas, which are generally smaller than the previously used involved-field radiation therapy guidelines [36, 37]. Proton therapy is highly conformal, allowing it to target the disease site while sparing nearby healthy tissues. While the data are limited for the use of protons in the treatment of DLBCL, some studies have shown promising outcomes with minimal toxicity. Sachsman et al [38] reported a 91% 2-year local control rate and no grade 3 or 4 radiation toxicities for patients with DLBCL treated with proton therapy, during the 38-month follow-up period. Plastaras et al [39] reported on 24 patients with primary mediastinal B-cell lymphoma treated with proton therapy and demonstrated only 1 local relapse.

Radiation Therapy as a Bridging Tool for CAR T-Cell Therapy

CAR T-cell therapy and radiation therapy can benefit patients with relapsed DLBCL; combining the two might yield promising results [15]. In fact, radiation therapy could serve as a successful bridging strategy for CAR T-cell therapy by several means: (1) Aggressive relapsed lymphomas are usually refractory to systemic therapy and may progress during CAR T-cell manufacturing (2-6 weeks), weakening the patient and reducing the response to CAR T-cell therapy as seen in the ZUMA-1 trial where approximately 10% of the patients did not receive the CAR-T product owing to disease progression among other reasons [11]. However, even chemoresistant lymphomas can demonstrate sensitivity to radiation [40], which can be used to control the disease during manufacturing. (2) Radiation can serve solely or in combination with chemotherapy as a lymphodepleting agent giving CAR T cells the needed space to work. (3) Radiation has been proven to sensitize solid tumors to immunotherapy [41, 42] and more recently, to provoke an abscopal-like effect to CAR T-cell therapy [43], suggesting its ability to enhance CAR T-cell activity. (4) Radiation can decrease the lymphoma tumor burden, which in turn may potentially decrease the cytokines released after the infusion of CAR T cells. This could, parenthetically, reduce the severity of CRS [28, 29, 44] and hence reduce the need for higher doses of steroids, which have lympholytic properties. (5) Some CAR T-cell candidates may have indications for radiation therapy. These include those that have symptomatically involved sites that need palliation, bulky disease, and limited area of relapsed lymphoma that can be encompassed in radiation fields. Radiation in these patients can serve a dual purpose.

Arscott et al [45] were the first to report the use of radiation as a bridge to CAR T-cell therapy. Five patients were bridged with radiation before tisa-cel infusion. They reported no grade 3 or higher CRS in those patients. Moreover, the 1-year progression-free survival among the patients who received radiation was better (78%) than among those who did not receive radiation (44%). Sim et al [46] bridged 12 patients with radiation before axi-cel infusion. They reported that 80% of the patients responded to radiation, and none had significant toxicities during bridging. Moreover, none had disease progression before CAR T-cell infusion [46]. Imber et al [47] reported as well excellent pre CAR local control and initial post CAR objective response rate (100%) after bridging 11 DLBCL patients with radiation. LaRiviere et al [44] prescribed bridging radiation therapy to 5 patients before CAR T-cell infusion. None of these patients developed grade 3 or higher CRS compared to 5 of 19 who did not receive prior radiation. There were no reported deaths (0 of 5) after 139 days of follow-up. Disease progression was seen in 2 of 5 patients who received radiation induction as compared to 10 of 19 who did not receive induction [44] (**Table**).

Table. Results of the studies that investigated the role of RT as a bridging strategy to CAR T-cell therapy.

Study	Arscott et al[45]	Sim et al[46]	Imber et al[47]	LaRiviere et al[44]
RT sample size	5	12	11	5
ORR, %	100 (1 y)	81.8 (median follow-up 3.3 mo)	100 (30 d)	N/A
PFS, %	78 (1 y)	N/A	N/A	N/A (2/5 progressed)
CRS incidence, %	0	27	45	40 (all grade 2)
CR, %	N/A	45	83 (5/6 at 30 d), 60 (3/5 at 90 d)	N/A

Abbreviations: RT, radiation therapy; CAR, chimeric antigen receptor; ORR, objective response rate; N/A, data not available; PFS, progression-free survival; CRS, cytokine release syndrome; CR, complete remission.

Since one of the main adverse events radiation can cause in these patients is blood dyscrasia [48], it is advised to perform apheresis before radiation to avoid lymphopenia. Data suggest lower success rates of CAR T-cell manufacturing with lower absolute lymphocyte count (generally defined as fewer than 100/μL) [49]. On the other hand, hematologic toxicity from radiation can be leveraged to help in lymphodepletion following the apheresis.

Role for Proton Therapy

To date no studies have reported the use of proton therapy as a bridging strategy to CAR T-cell therapy. As previously described, standard radiation therapy using photons may help to decrease CAR T-cell therapy–related toxicities and, thus far, has been associated with low rates of radiation-related toxicity. However, in some situations, based on disease distribution (eg, mediastinal involvement) and radiation dose, patients could be at risk of radiation-related toxicities such as pneumonitis [50], colitis, esophagitis, mucositis, and xerostomia that might cause the patient or physician to decline such treatment. In fact, the ILROG report on proton therapy for mediastinal lymphomas recommends consideration of proton therapy for "heavily pretreated patients who are at higher risk for radiation-related toxicity to the bone marrow, heart, and lungs [51]." Unfortunately, it is not clear why so few patients receive radiation therapy as bridging treatment to CAR T-cell therapy and we can only hypothesize that fear of radiation therapy toxicity may contribute. In that scenario, proton therapy can be used to reduce the radiation dose to the organs at risk for patients with lymphomas, yielding similar disease outcomes, though potentially with fewer side effects than photon-based radiation therapy [38, 52]. This may be more critical for those with disease located in the mediastinal region, where pneumonitis could be a significant factor.

Additionally, lymphopenia can occur following radiation therapy, and lymphopenia has been shown to be a prognostic factor for successful collection and manufacturing of CAR T cells. Avoiding radiation therapy before leukapheresis of T cells is strongly encouraged. If radiation is needed urgently before leukapheresis, proton therapy may reduce the impact on absolute lymphocyte count. Among patients with esophageal cancer and lung cancer receiving radiation therapy, lymphopenia occurs less often with proton therapy than with IMRT [53, 54]. Since protons have similar control rates with the potential for reduced side effects, compared to other forms of radiation therapy, the use of protons as a bridging strategy for CAR T-cell therapy may reduce side effects, augment response, or both. Future trials and studies are needed to validate this hypothesis.

While proton therapy may offer some hypothetical benefit for patients, it may also be inferior in some ways. As previously mentioned, IMRT may contribute more to lymphopenia, which may actually be helpful during manufacturing in an effort to make room for eventual CAR T-cell infusion. Additionally, proton therapy could contribute to the rising cost of treatment, which is already quite substantial with CAR T-cell treatment [55]. Therefore, careful exploration for using proton therapy in CAR T-cell treatment is needed, such as on a clinical trial or registry [56].

Conclusion

CAR T-cell therapy represents one of the most innovative and revolutionary treatments for R/R large B-cell lymphoma. Using radiation therapy as a bridging technique could reduce CAR T-cell therapy–related toxicity and increase the number of patients that will reach the infusion phase of treatment. This is due to the ability of radiation to lymphodeplete, cytoreduce, debulk, stabilize, and sensitize the tumor. Proton therapy can serve as an alternative to the standard radiation therapy to further minimize radiation-related toxicities, making it a promising bridging strategy for CAR T-cell therapy in DLBCL for some patients.

ADDITIONAL INFORMATION AND DECLARATIONS

Conflicts of Interest: The authors have no relevant conflicts of interest to disclose.

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