Concurrent application of blinatumomab and haploidentical donor leukocyte infusions for refractory primary mediastinal large B-cell lymphoma

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Abstract

Primary mediastinal large B-cell lymphoma (PMBCL) is a rare hematologic malignancy with distinct clinical and immunopathological features. We report a case of a young adult male with disease refractory to multiple lines of therapy, including CAR-T cells, who achieved his first complete remission after haploidentical BMT, following donor leukocyte infusions (DLI) given concurrently with blinatumomab. While DLI has been used after T-replete haplo-BMT with PT-CY, there are no reports on its use for PMBCL. Similarly, blinatumomab is active against B-cell lymphomas, but literature is lacking in patients with PMBCL. Our experience illustrates that blinatumomab can be used concurrently with DLI in a haploidentical setting to achieve disease response in PMBCL. Despite our encouraging experience with this case, we would not recommend this approach outside of a clinical trial as blinatumomab may exacerbate the GvHD risks of DLI especially in a haploidentical setting.

ABSTRACT

Primary mediastinal large B-cell lymphoma (PMBCL) is a rare hematologic malignancy with distinct clinical and immunopathological features. We report a case of a young male with disease refractory to multiple lines of therapy, including CAR-T cells, who achieved his first complete remission after haploidentical BMT, following donor leukocyte infusions (DLI) given concurrently with blinatumomab. While DLI has been used after T-replete haplo-BMT with PT-CY, there are no reports on its use for PMBCL. Similarly, blinatumomab is active against B-cell lymphomas, but literature is lacking in patients with PMBCL. Our experience illustrates that blinatumomab can be used concurrently with DLI in a haploidentical setting to achieve disease response in PMBCL. Despite our encouraging experience with this case, we would not recommend this approach outside of a clinical trial as blinatumomab may exacerbate the GvHD risks of DLI especially in a haploidentical setting.

Primary mediastinal large B-cell lymphoma (PMBCL) is a rare hematologic malignancy representing only 2-3% of non-Hodgkin lymphomas (NHLs)[1]. It has distinct clinical and immunopathological features intermediate to diffuse large B-cell (DLBCL) and Hodgkin lymphomas. It is characterized by bulky, locally invasive disease that can infiltrate the lungs, pleura, chest wall and pericardium, often compromising the airway and venous blood flow. While prognosis is generally favorable, especially for younger individuals, those who relapse have a dramatically lower chance of survival.

A 21-year-old male presented with left cervical swelling and pain over his clavicle. A CT of his chest and abdomen was obtained, showing a large anterior mediastinal mass. Pathologic and immunohistochemical examination showed fibrotic tissue with nests of large CD10- CD30- BCL6+ MUM1+ PAX5+ B-cells with loss of surface immunoglobulin expression and expression of CD19, CD20, CD23 and PD-L1 and a Ki-67 proliferative index of 90%, confirming the diagnosis of PMBCL, non-germinal center type. The cells were negative for rearrangement of cMYC, BCL2 and BCL6 translocation by fluorescence in situ hybridization.

Upon diagnosis, he received six cycles of dose adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab (DA-EPOCH-R)[2]. An end of treatment PET-CT scan demonstrated refractory disease, necessitating involved field irradiation. A follow-up PET-CT scan revealed extension of disease below the diaphragm **(Figure 1A)** . The patient then received salvage chemotherapy of ifosfamide, carboplatin, etoposide and rituximab (ICE-R), but his disease progressed. A cycle of rituximab, gemcitabine, navelbine and doxorubicin (R-GND) was given for debulking and pembrolizumab was initiated with an early response **(Figure 1B).**However, his disease again demonstrated progression following eight cycles of pembrolizumab **(Figure 1C)** . A repeat biopsy demonstrated that the tumor developed expression of CD30 in a diffuse and strong membranous fashion, leading to treatment with brentuximab vedotin resulting in a partial response (PR) **(Figure 1D)** . He then received an infusion of CAR-T cells (Tisagenlecleucel), but his disease progressed **(Figure 1E)** . Subsequent treatments included bendamustine and brentuximab followed by gemcitabine, cisplatin and dexamethasone, again yielding a very good PR **(Figure 1F)** .

Having completed nine failed radiochemoimmunotherapy regimens, he consented to a T-replete haploidentical bone marrow transplantation (haplo-BMT) with his brother as the donor. He was conditioned with a myeloablative regimen of busulfan, fludarabine and melphalan with post-transplant cyclophosphamide (PT-CY)[3-5]. He showed no clinical signs of acute graft-versus-host disease (aGvHD) despite maintaining low tacrolimus levels (4-6 ng/ml) during the first month post-BMT. Early tacrolimus taper was started on day +33 with discontinuation on day +40. On day +44, a suprasternal chest wall mass emerged and a repeat biopsy on day +47 confirmed PMBCL. A PET-CT scan on day +49 demonstrated interval progression of disease **(Figure 2a)** .

Blinatumomab infusion was initiated on day +50 at a dose of 10 $\mu g/m^2$/day, escalated to 15 $\mu g/m^2$/day on day +52. While on blinatumomab (day +54), the patient received a haploidentical DLI from the same donor at a dose of $3x10^6$ $CD3^+$ cells/kg. His chest wall mass continued to expand with intensifying pain, so, two weeks later, he was given a second DLI infusion consisting of $1x\ 10^7 CD3^+$ cells/kg (day +68). On day +78, the patient developed a stage I aGvHD skin rash, and, upon exam, his chest wall mass was noticeably smaller. aGvHD progressed to stage II skin on day +82 and he started topical steroids. A repeat PET-CT scan on day +85 showed a mixed response with decreased mediastinal and chest wall FDG avidity but new focal subpleural avid areas, new mildly avid pulmonary nodules and a new focal lesion in the hepatic dome **(Figure 2b)** . On day +89, his aGvHD had progressed to stage III with vomiting, diarrhea and weight loss. Therefore, prednisone 2 mg/kg and cyclosporine were started. With progression of GvHD his chest mass and lymphadenopathy resolved. A repeat PET-CT scan on day +113 confirmed a sustained tumor response and revealed intense FDG uptake throughout the small and large colon compatible with intestinal GvHD **(Figure 2C)** . After initial improvement of skin and GI aGvHD symptoms cyclosporine was decreased in order to optimize graft-versus-lymphoma (GvL) effects. Drug levels were kept subtherapeutic (mean of 50 ng/ml) from day +110 until day +150, at which time it was discontinued. Likewise, prednisone was progressively tapered to 1 mg/kg by day +120 and discontinued on day +160. A repeat PET-CT scan was performed on day +167, after 4 cycles of blinatumomab, which demostrated, for the first time since his diagnosis, a complete metabolic response of his PMBCL with less intestinal FDG uptake due to aGvHD **(Figure 2D)** . Unfortunately, two months after completing blinatumomab the patient noted increasing lympadenopthy and repeat PET-CT confirmed extensive relapse of his PMBCL **(Figure 2E)** .

DA-EPOCH-R has been used frequently as front-line treatment of PMBCL, but, due to the rarity of the disease, there is no consensus on optimal consolidation or treatment for relapsed/refractory disease. Many of the agents our patient received have been used previously for relapsed/refractory PMBCL[2, 6-9]. In contrast to our patient who failed to respond to anti-CD19 CAR-T cell therapy, there is a single recent report of a patient with PMBCL who achieved a CR[10]. It is also important to note that FDA approval for tisagenlecleucel is for DLBCL and not PMBCL, however, it was decided to treat our patient due to lack of other promising options.

Autologous HCT has traditionally been used as salvage therapy for NHL. Our patient did not undergo an autologous HCT as he did not have chemotherapy sensitive disease. A recent four-institution retrospective

analysis reviewed the outcomes of 28 patients with relapsed/refractory PMBCL who received allogeneic HCT[11]. Eighty percent of patients were sensitive to pre-transplant therapy. The 5-year progression-free and overall survivals were 34% and 45%, respectively. None of the patients received prior PD-1 blockade or CAR-T cells and none received haploidentical HCT as was the case with our patient who had received all three. Despite having been treated with a PD-1 inhibitor before his transplant, receiving myeloablative conditioning and having his tacrolimus levels purposefully maintained in the low therapeutic range and discontinued by day +40, the patient did not develop aGvHD. Recent studies have documented that PT-CY lowers the risk of GvHD in patients that have received checkpoint inhibitors[12].

DLI has been used after T-replete haplo-BMT with PT-CY against relapsed leukemia and NHL, but there are no reports employing DLI for PMBCL[13]. Blinatumomab has shown activity against other B-cell lymphomas, but there are no published reports in patients with PMBCL[14]. The most effective dose of blinatumomab for NHL is 4-fold higher (60 $\mu g/m^2$/day) than what our patient received as his dose was restricted due to ongoing peripheral neuropathy and persistent headaches. There is a single case report on concomitant use of DLI with blinatumomab following a matched unrelated donor transplant for leukemia but no reports in haploidentical HCT[15]. While our experience illustrates that blinatumomab can be used concurrently with DLI in a haploidentical setting, the relative contribution of DLI versus blinatumomab in achieving a metabolic CR was not clear. Our patient relapsed after stopping blinatumomab, however his GvHD symptoms had also resolved and therefore GvL activity had likely subsided as well. Although our patient's response to blinatumomab and DLI was short-lived, it was the only therapy to induce a complete remission as his PMBCL had been refractory to numerous lines of therapy, including to anti-CD19 CAR-T cells. Despite our encouraging experience with this case, we would not recommend this strategy outside a clinical trial as blinatumomab may exacerbate the GvHD risks of DLI especially in a haploidentical setting. Formally studying this treatment combination in high-risk patients may be meaningful.

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Authorship Contributions:

J.S. reviewed the clinical records and wrote the manuscript. AK edited the manuscript and treated the patient. E.K. co-wrote the manuscript and managed the patient during his cell therapies and transplantation.

Disclosure of Conflicts of Interest:

There are no conflicts of interest, financial or otherwise, involving any of the authors regarding the submission or publication of this manuscript.

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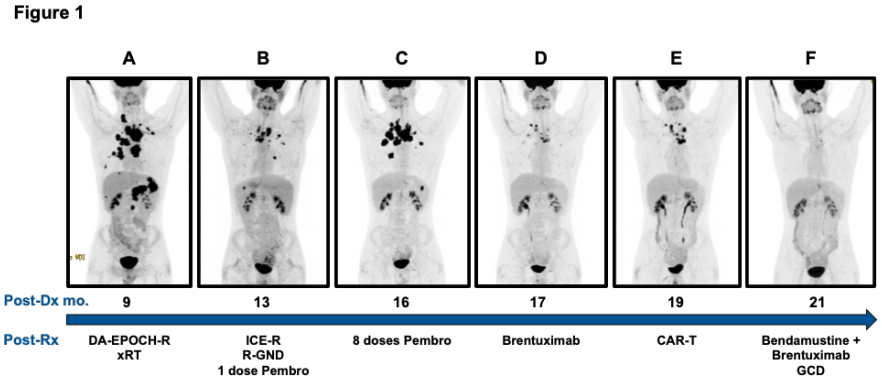

Figure 1. Responses to treatment before haploidentical-BMT. Shown are PET-CT images performed after each respective treatment (Post-Rx). Post-Dx mo. indicate months after initial diagnosis. (A) extension of disease below the diaphragm following dose adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab (DA-EPOCH-R) and involved field irradiation; (B) interim response after receiving ifosfamide, carboplatin, etoposide and rituximab (ICE-R), then navelbine and doxorubicin (R-GND) followed by first dose of pembrolizumab; (C) progression of disease after eight doses of pembrolizumab; (D) partial response after brentuximab vedotin; (E) failure to respond to anti-CD19 CAR-T cell therapy; (F) very good partial response after bendamustine and brentuximab followed by gemcitabine, cisplatin and dexamethasone (GCD).

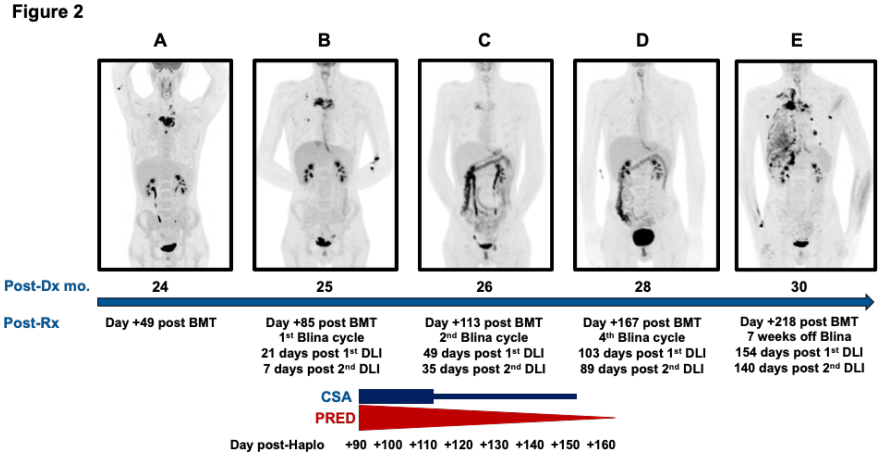

Figure 2. Responses to treatment after haploidentical-BMT. Shown are PET-CT images performed after each respective treatment (Post-Rx). Post-Dx mo. indicate months after initial diagnosis. (A) disease progression after haplo-BMT; (B) mixed response with decreased mediastinal and chest wall FDG avidity but new focal subpleural avid areas, new mildly avid pulmonary nodules and a new focal lesion in the hepatic dome during second cycle of blinatumomab (Blina) and following DLI but before progression to grade III GvHD; (C) sustained tumor response with intense FDG uptake throughout the small and large colon compatible with intestinal graft versus host disease while on tapering doses of prednisone and cyclosporine A; (D) complete metabolic response with less intestinal FDG uptake but evidence of esophangitis and gastritis after discontinuing immunosuppression; (E) disease recurrence after stopping blinatumomab and resolution of GvHD

Figure 1

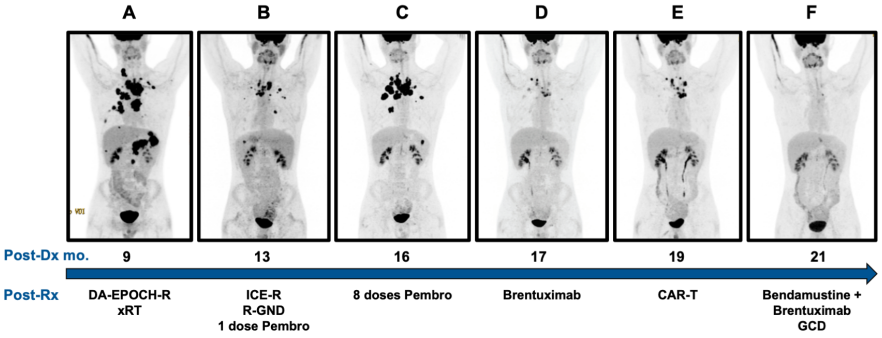

Figure 2