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Case Report

Combination of Donor Lymphocyte Infusion and Blinatumomab for B-Cell Lymphoblastic Lymphoma Relapse after Allogeneic Stem-Cell Transplantation

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Keywords

Blinatumomab · Donor lymphocyte infusion · B-cell lymphoblastic lymphoma · Allogeneic stem-cell transplantation

Abstract

A woman in her forties with relapsed B-cell lymphoblastic lymphoma was treated with blinatumomab, but the drug proved ineffective. Salvage therapy with clofarabine induced a complete remission, and she received an allogeneic stem-cell transplantation (allo-SCT) from an HLA-matched sibling donor. However, her disease relapsed only 4 months after the allo-SCT. Three courses of combination therapy with donor lymphocyte infusion (DLI) and blinatumomab were administered, and the tumor progression was well controlled for 6 months, leading to a second allo-SCT from an HLA-haploidentical donor. The remission was persistent for approximately 1 year, but the disease relapsed in her central nervous system, and she eventually died. Our case demonstrated the efficacy and safety of concomitant use of DLI and blinatumomab. This combination presumably enhanced a graft-versus-lymphoma effect of allogeneic T-cells without provoking graft-versus-host disease.

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Introduction

Although various treatment options have been tried and tested for acute lymphoblastic leukemia in patients who have relapsed after allogeneic stem-cell transplantation (allo-SCT), the prognosis of these patients remains dismal [1]. Donor lymphocyte infusion (DLI) is a conventional approach for these patients, and it has an approximately 16–40% complete response rate [2]. However, most of the patients have relapsed after DLI, and the results of the treatment alone are still unsatisfactory. Blinatumomab, a bispecific CD19-directed CD3+ T-cell engager, is an established drug for patients with relapsed/refractory acute lymphoblastic leukemia [3, 4]. In the post-allo-SCT setting, recent reports have also shown the potential benefits of blinatumomab in directing allogeneic CD3+ T-cells to residual or relapsed CD19+ leukemia cells and enhancing the graft-versus-leukemia/lymphoma effect without exacerbating graft-versus-host disease (GVHD) [5, 6]. A few case reports also describe the concurrent use of DLI and blinatumomab and the promising results [7–11]. Here, we present a case of B-cell lymphoblastic lymphoma (B-LBL) where blinatumomab was ineffective before allo-SCT, but a combination of DLI and blinatumomab was effective in the posttransplantation recurrence period.

Case Report

In X-3 years, a woman in her forties visited the hospital with a complaint of back pain. A CT scan revealed a tumor in her left eighth limb. A physician performed a biopsy, and the woman was diagnosed with diffuse large B-cell lymphoma based on the pathological examination. She moved to our hospital for treatment initiation. She was treated with eight cycles of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). A PET-CT scan revealed an accumulation of fluorodeoxyglucose in the lesion, and we therefore performed involved-field radiation therapy, resulting in a complete metabolic remission. However, X-2 years later, systemic nodules emerged. The pathological examination, using a biopsy sample from her left breast, showed diffusely proliferated large cells with immature nuclei, with positivity for terminal deoxynucleotidyl transferase, CD10, CD19, and CD79a, indicating B-LBL. We examined her cerebrospinal fluid and found no evidence of central nervous system (CNS) invasion. As a CNS prophylaxis, we administered 12 mg of methotrexate intrathecally. We initiated 28 μg per day of blinatumomab as salvage therapy but stopped it on the 15th day due to rapid enlargement of multiple tumors. Administration of 52 mg/m^2 clofarabine for 5 days induced a complete remission. In X-1 year, the patient received an allo-SCT from an HLA-matched sibling donor, preceded by a myeloablative conditioning regimen consisting of cyclophosphamide and total body irradiation. Short-term methotrexate and cyclosporine were used as prophylaxis of GVHD. Unfortunately, 4 months after the transplantation, subcutaneous tumors reappeared in her right back, shoulder, and the posterior portion of the left auricle, and relapse was confirmed by a biopsy of the right back tumor. Bone marrow chimerism was at 99.2% of the donor type at the time. We immediately stopped the administration of the immunosuppressant and administered three courses of combination therapy with DLI and blinatumomab (Fig. 1). With this treatment combination, tumor progression was controlled for 6 months, although there was indeed a slight increase in tumor size. Except for a low-grade fever during the third course of treatment, no adverse events and GVHD were observed. The subsequent treatment with clofarabine and cytarabine resulted in almost complete disappearance of systemic tumors on CT scan, except for the tumors in the posterior auricle. After administration of the conditioning regimen – including fludarabine, melphalan, cytarabine, and 4 Gy total body

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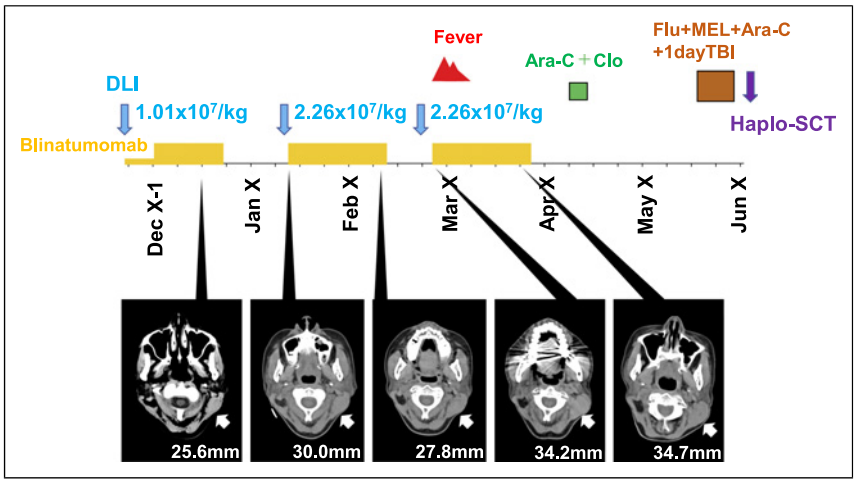

Fig. 1. Treatment course of DLIs and blinatumomab. Three cycles of combination therapy of DLIs and blinatumomab. The black arrows and the numbers represent infusions of donor lymphocytes and their cell doses, respectively. The horizontally striped boxes represent the administration of blinatumomab. For the first week of the first cycle, 9 μg/day was administered, followed by 28 μg/day. The CT scan images of a lesion in the posterior portion of the left auricle and its long axis length at each time point are shown. Ara-C, cytosine arabinoside; Clo, clofarabine; DLI, donor lymphocyte infusion; Flu, fludarabine; Haplo-SCT, HLA-haploidentical stem-cell transplantation; MEL, melphalan; TBI, total body irradiation.

irradiation – she underwent a second allo-SCT from an HLA-haploidentical related donor, receiving tacrolimus, low-dose (2.5 mg/kg) rabbit anti-thymoglobulin, and methyl prednisolone as prophylaxis for GVHD. After transplantation, she remained disease-free without any severe complications for 12 months. However, she developed thrombotic microangiopathy, and her renal function rapidly deteriorated to the point that she required hemodialysis. During treatment for thrombotic microangiopathy, loss of consciousness occurred, and a head MRI revealed multiple masses with high signal intensity on diffusion-weighted images and low signal intensity on T2-weighted images. Those lesions were associated with peripheral edema and partial hemorrhage; the proximal ventricles appeared compressed. MR angiography showed no cerebral vascular defects. These findings suggested that the lymphoma relapsed in the CNS. In consultation with her family, we decided to switch to the best supportive care; she died 2 days later.

Discussion

In the present case, the combination therapy of blinatumomab and DLI allowed us to successfully bridge to the second transplantation. A few previous reports have documented the potential efficacy of this combination therapy in patients with posttransplantation relapse (Table 1) [7–11]. However, in a previous study [11], blinatumomab and DLI were used in combination with chemotherapy, which made it difficult to assess the efficacy of blinatumomab and DLI. Since the other studies have not described whether blinatumomab was used before transplantation [7–10], it is not possible to compare the effect of blinatumomab before and after transplantation. However, in the present case, blinatumomab had no effect before transplantation but did after transplantation, suggesting that allogeneic T-lymphocytes engaged by blinatumomab suppressed the tumors to which the patient's original T-lymphocytes did not respond. We believe that DLI enhanced the effects of blinatumomab, although it was

Table 1. Previous studies reporting the concurrent use of DLI and blinatumomab

Type of diseases	Patients, *N*	Best response	Duration of response (outcomes)	References
B-ALL	4	CR = 3, PD = 1	15 Months (EM and BM relapse) 13 Months (continued CR) 7 Months (continued CR) 7 Months (continued progression of EM disease)	Ueda et al. 2016 [7]
B-ALL	1	CR	10 Months (death due to treatment -related mortality)	Nachmias et al. 2018 [8]
MPAL	1	CR	15 Months (continued CR)	Durer et al. 2019 [9]
B-ALL	1	CR	Not described (relapse)	Ampatzidou et al. 2020 [10]
B-ALL	1	CR (combined with clofarabine)	2 Months (relapse in CSF)	Choi et al. 2021 [11]

B-ALL, B-cell acute lymphoblastic leukemia; BM, bone marrow; CR, complete remission; CSF, cerebrospinal fluid; EM, extramedullary; MPAL, mixed phenotypic acute leukemia; PD, progressive disease.

not possible to evaluate in this case. A recent phase 2 study assessing blinatumomab for post-allo-SCT maintenance showed that a greater number of CD3+ T-cells were associated with a higher response rate [5], suggesting that the supply of CD3+ T-cells by DLI augments the effect of blinatumomab. No severe adverse events or GVHD were observed in this case, as in previous studies. The addition of DLI to blinatumomab is feasible and might be a promising approach for unfit patients or candidates for re-transplantation who want to avoid organ damage. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000531834).

Statement of Ethics

This study was reviewed and approved by the Institutional Review Board of Jyoban Hospital, approval number JHTF-2019-003. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images prior to their passing away.

Conflict of Interest Statement

All authors have no conflicts of interest to declare.

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Author Contributions

Jinichi Mori designed the study and wrote the manuscript. Naoki Shingai, Takeshi Kobayashi, and Noriko Doki supervised the study. All authors reviewed and approved the final version of the manuscript.

Data Availability Statement

Although consent for information disclosure has been obtained from the patient, it contains sensitive personal information. Therefore, the medical record will be provided upon request by contacting the corresponding author.

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