

Successful second allogeneic stem-cell transplantation from the same sibling donor for a patient with recurrent hepatosplenic gamma-delta (γ/δ) T-cell lymphoma

A case report

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Abstract

Rationale: Hepatosplenic T-cell lymphoma (HSTCL) is a rare but aggressive type of peripheral T-cell lymphoma (PTCL). There is an urgent need for effective treatment due to the poor prognosis of HSTCL. Here, for the 1st time we describe the rare successful case of HSTCL who relapsed after a previous allogeneic stem-cell transplantation (allo-SCT), achieved remission with the second allo-SCT from the same donor.

Patient concerns: A 24-year-old male, presented with a 2-week history of fever, drenching night sweats and nonquantified weight loss.

Diagnoses: Laboratory studies, flow cytometry of immunophenotyped, and physical examination results strongly suggested hepatosplenic γ/δ T-cell lymphoma, stage IVB.

Interventions: We proceeded to an allo-SCT with a human leukocyte antigen (HLA) identical sibling donor. The bone marrow examination and fluorescent in situ hybridization were observed for complete donor chimerism of bone marrow cells on day 34. On day 157 after the initial allo-SCT, the bone marrow examination revealed the relapse of the sinusoidal infiltration with lymphoma cells. Considering the disease persistence, we conducted the second allo-SCT from the same HLA-identical sibling donor immediately.

Outcomes: Bone marrow examination indicated hematologic recovery without residual lymphoma cells.

Lessons: Our encouraging outcome suggests that the latter allo-SCT needs to be considered early for patients with disease recurrence, and it also demonstrates that graft-vs-lymphoma conferred by allo-SCT may play an essential role on HSTCL treatment. Furthermore, detecting related genes at diagnosis may have prognostic implications and guidance value for personal chemotherapy program.

Abbreviations: allo-SCT = allogeneic stem-cell transplantation, Ara-C = cytosine arabinoside, CCNU = lomustine, CsA = cyclosporine, FLU = fludarabine, GVL = graft-vs-lymphoma, GVHD = graft-vs-host disease, HLA = human leukocyte antigen, HSTCL = hepatosplenic T-cell lymphoma, MMF = mycophenolate mofetil, MTX = short-course methotrexate, PTCL = peripheral T-cell lymphomas.

Keywords: allogeneic stem-cell transplantation, hepatosplenic γ/δ T-cell lymphoma, hepatosplenic T-cell lymphoma

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HP and JH contributed equally to this work.

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1. Introduction

Hepatosplenic T-cell lymphoma (HSTCL) is a rare but aggressive type of peripheral T-cell lymphoma (PTCL). HSTCL has a typical immunophenotype (CD2⁺, CD3⁺, CD4⁻, CD5⁻, CD7⁺, CD8⁻)^[1] and common cytogenetic abnormalities that include isochromosome 7q, sometimes accompanied by trisomy 8. It consists of 2 subtypes: a standard form with expression of γ/δ T-cell receptor (TCR) chain and a rarer form with expression of the α/β TCR chain.^[2] It is characterized by thrombocytopenia, hepatosplenomegaly, systemic symptoms and an absence of lymphadenopathy, and it occurs predominantly in young men.

The HSTCL is an almost invariably fatal disease characterized by a chemo-refractory, unremitting clinical course and a 5-year overall survival of <10%.^[3] Therefore, there is imperative need for an effective treatment. A study by Tanase et al stated that the graft-vs-lymphoma (GVL) effect conferred by allogeneic stem-cell transplantation (allo-SCT) could lead to long-term survival in a proportion of patients with HSTCL.^[4] Remissions following donor lymphocyte infusion and reduced immunosuppression suggest potent GVL effects.^[5,6] Here, we describe a rare successfully treated patient with HSTCL who relapsed after the initial allo-SCT and achieved remission with the second allo-SCT from the same donor. This is the 1st report of this kind to date.

2. Case report

A 24-year-old male of Chinese origin presented with a 2-week history of fever, drenching night sweats, and nonquantified weight loss. No contributory family or social history was elicited. Physical examination found massive hepatosplenomegaly, without lymphadenopathy. Laboratory studies were remarkable, with a hemoglobin level of 8.5 g/dL, platelet of 930/L, elevated lactate dehydrogenase of 2069 IU/L. Liver function tests were mildly elevated. HCV viral load was undetectable. Human immunodeficiency virus/Epstein-Barr virus/cytomegalovirus (HIV/EBV/CMV) serology was negative. The morphology of the patient's bone marrow presented hypercellular infiltration by atypical lymphoid cells (Fig. 1A). Flow cytometry of immunophenotype showed that the cells were positive for CD2, CD3, CD7, CD11b, CD11c, CD16, CD38, and TCR gamma-delta (γ/δ) and negative for CD4, CD5, CD8, CD19, CD20, CD22, CD56, CD57, and TCR alpha-beta (α/β). Molecular analysis demonstrated TCRs with gamma-delta rearrangements. These results strongly suggested the diagnosis of hepatosplenic γ/δ T-cell lymphoma, stage IVB.

He underwent chemotherapy (ECHOP, VDLP, and DHAP regimens, respectively) but without improvement of his clinical picture. Hepatosplenomegaly and liver dysfunction were persisted. A repeat bone marrow examination demonstrated approximately 85% persistent disease involvement. Having evidence of the lymphoma's refractoriness and considering the patient's young age, an allo-SCT with a human leukocyte antigen (HLA)-identical sibling donor had to be carried out. The myeloablative conditioning regimen consisted of lomustine (CCNU 200 mg/m² day 11 before allo-SCT), fludarabine (FLU 30 mg/m² day 10, 9, 8, 7 before allo-SCT), cytosine arabinoside (Ara-C 2 g/m² day 10, 9, 8, 7 before allo-SCT), busulfan (Bu 0.8 mg/kg every 6 hours day 6, 5, 4 before allo-SCT), and cyclophosphamide (CY 50 mg/kg day 3, 2 before allo-SCT), with reinfusion of 10.8×10^8 /kg of monocytes and 9.6×10^6 /kg of CD34⁺ bone marrow stem cells. Graft-vs-host disease (GVHD)

prophylaxis included cyclosporine (CsA), mycophenolate mofetil (MMF), and a short-course methotrexate (MTX). Hematopoietic reconstitution occurred without difficulty: thrombocytes engrafted on day +14 and neutrophils engrafted on day +15. On day 34 after allo-SCT, the bone marrow examination revealed no evidence of lymphoma cells (Fig. 1B); fluorescence in situ hybridization demonstrated complete donor chimerism of bone marrow cells. He did not show any sign of acute GVHD. Only 1 acute complication was an episode of hemorrhagic cystitis, which was successfully dealt by a series of treatments. The patient was completely asymptomatic during the follow-up period of 6 months.

On day 157 after the initial allo-SCT, the bone marrow examination confirmed the relapse of the sinusoidal infiltration with lymphoma cells (Fig. 1C, D). Lymphoma with an MDR phenotype is associated with a highly aggressive clinical course and a poor prognosis.^[7,8] To determine the correlation between related gene expression and therapeutic efficacy, we measured the expression of P-gp, MRP-1, BCRP, LRP, Aurka inhibitor, SYK inhibitor, ID3, and c-MYC; however, none of them were expressed. Considering the disease persistence, we immediately conducted a second allo-SCT from the same HLA-identical sibling donor. The patient was administered total body irradiation (4.5 GY 5, 4), CY (60 mg/kg 3, 2), CsA, MMF, and a short-course of MTX as GVHD prophylaxis. The preparative regimen was well tolerated, and mononuclear cell counts were 13.37×10^8 /kg. G-CSF-supported neutrophils were engrafted on day 16. We terminated CsA and MMF to avoid medication-induced liver lesion. The patient developed multiple organ dysfunction syndrome secondary to infection, which was successfully treated by steroid and antibiotics. Immunosuppression with tacrolimus (0.03 mg/kg) was reinstated on day 62, and thrombocytes were engrafted on day 94 with no evidence of acute GVHD. Bone marrow examination indicated hematologic recovery without residual lymphoma cells.

3. Discussion

Our patient underwent a second allo-SCT from the same sibling donor, to which he responded with a complete remission. It appears that a second allo-SCT may be a promising option for patients with relapsed lymphoma following a prior transplantation. Since we used the same donor for the 1st and 2nd allo-SCTs, with similar immunologic background and HLA disparity, we can speculate about the feasibility and effectiveness of the second allo-SCT. Compared with the 1st allo-SCT, withdrawal of immunosuppression and the appearance of cGVHD in the later allo-SCT contributed to a GVL effect. Our patient seemed to be sensitive to immunologically mediated cytotoxicity, as seen in other cases over the last few years.^[4,9]

Specific gene expression seems to have an important impact on the treatment outcomes and prognosis of HSTCL. Lymphoma with an MDR phenotype is associated with a highly aggressive clinical course and a poor prognosis. The expression of P-gp, MRP-1, BCRP, and LRP has been demonstrated to play a role in chemotherapy resistance in hematopoietic neoplasia.^[7,8] We tested the above 4 proteins in our study and obtained negative results. Furthermore, oncogenes, highly expressed in T-cell lymphoma cell lines, related to inadequate therapeutic efficacy and worse prognosis, were not expressed in our patient. We also detected SYK and Aurka before the second allo-SCT. Aurka inhibitor (alisertib) and SYK

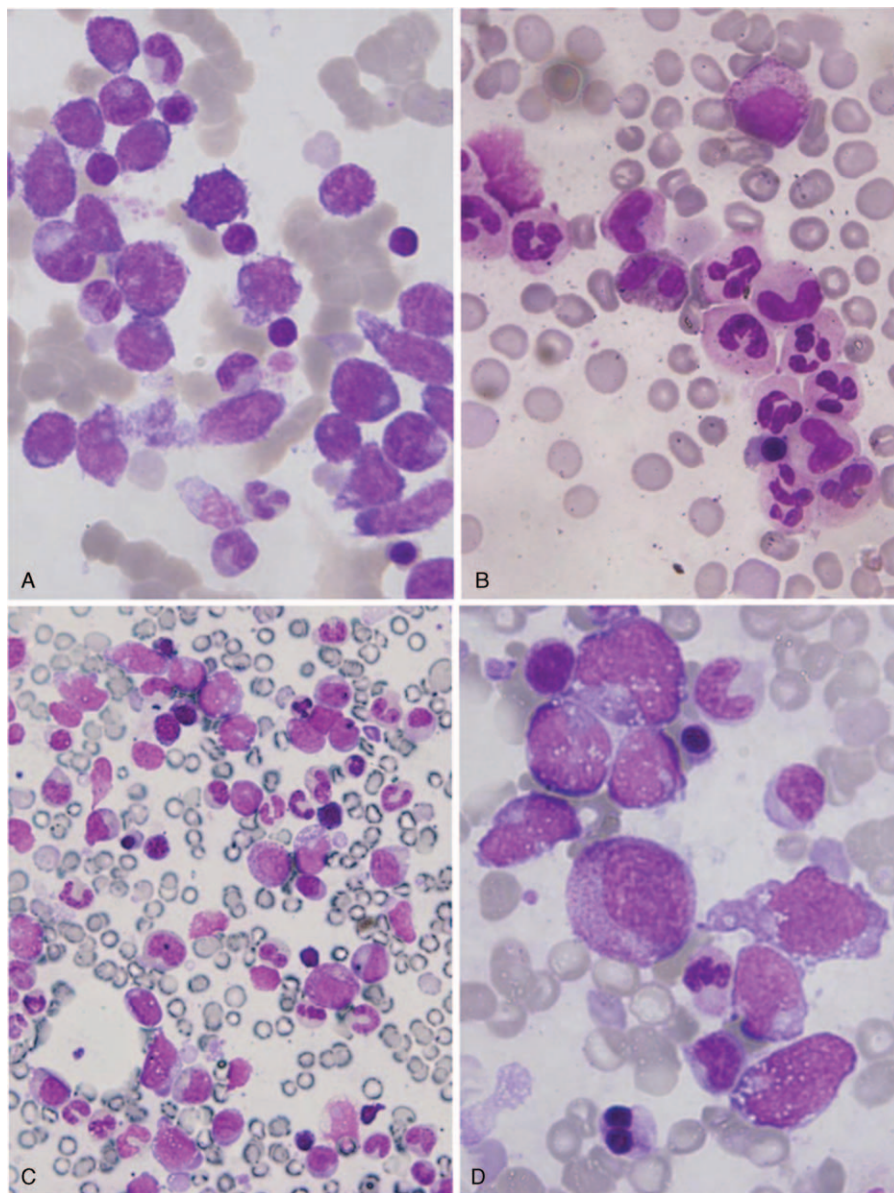


Figure 1. Bone marrow aspiration smear of patient's pro- and post-allogeneic stem-cell transplantation (allo-SCT). (A) An abnormal blastic monotypic lymphocyte population at the time of diagnosis of hepatosplenic T-cell lymphoma (Wright staining, original magnification $\times 1000$). (B) No evidence of lymphoma cells after the first allo-SCT (Wright staining, original magnification $\times 1000$). (C) A sinusoidal infiltrate composed of medium-sized atypical lymphocytes on day 157 after the 1st allo-SCT (Wright staining, original magnification $\times 400$). (D) Clusters of medium-sized lymphocytes with large pale and basophilic cytoplasm and no granules; irregular nuclear contours; and small nucleoli (Wright staining, original magnification $\times 1000$).

inhibitors have been shown to be beneficial in cancer chemotherapy and are well tolerated in patients with T-cell lymphoma.^[10] In light of the negative results, these new therapeutic agents were not considered in our patient. Additionally, ID3 and c-MYC, deemed to play an important role in the pathogenesis of HSTCL,^[11] were not detected in our case. These findings suggest that successful treatment with a second allo-SCT in our patient may be related to the lack of expression of multidrug resistance proteins and oncogenes.

Our study had a few limitations. First, it is a single case report. Collaboration with other centers to increase the case numbers would add to the validity of the study. Unfortunately, multicenter cooperation is still a great challenge for us, and there are problems we could not solve at present in the process. In addition, we only tested for major mutations previously reported and

clinically recognized, leading to the inadequate analysis of other potentially mutated genes.

4. Conclusion

In summary, the relapse of patients with HSTCL is usually associated a severe clinical condition and a fast-growing tumor. Our encouraging outcome suggests that a second allo-SCT needs to be considered early for patients with disease recurrence. It also demonstrates that GVL conferred by allo-SCT may play an important role in treating HSTCL. In addition, detecting related genes at diagnosis may have prognostic implications and guidance value for personal chemotherapy programs. These results suggest that future studies are required to assess the efficacy and safety of the treatment mentioned above in a larger cohort of patients with this rare disease.

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Author contributions

HP, JH, JNL, LY, and LW performed research. JYW, XW, LL, ZSY, and LW contributed viral new reagents. HP and JH designed and made the study, analyzed the data and wrote the paper.

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