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Case Report

Haploidentical Stem Cell Transplantation Using Post-Transplant Cyclophosphamide for T-Cell Prolymphocytic Leukemia after Alemtuzumab Induction Therapy: A Case Report

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Keywords
Haploidentical stem cell transplantation · Post-transplant cyclophosphamide · T-cell prolymphocytic leukemia · Alemtuzumab

Abstract
T-cell prolymphocytic leukemia (T-PLL) is a rare aggressive disease with a poor prognosis. Allogeneic stem cell transplantation (allo-SCT) followed by alemtuzumab administration is the most promising treatment for T-PLL but is associated with a high risk of infections as alemtuzumab strongly suppresses cellular immunity, leading to high transplant-related mortality and unsatisfactory survival rates. In addition, for patients without human leukocyte antigen-matched donors, haploidentical stem cell transplantation (haplo-SCT) using post-transplant cyclophosphamide (PTCy) has been used because of the ready availability of donors and achievement of results comparable to those of transplantation with human leukocyte antigen-matched donors. However, there are no reports on the efficacy and safety, including infectious complications, of haplo-SCT with PTCy after alemtuzumab therapy in patients with. Here, we describe a 66-year-old Japanese male patient with T-PLL treated successfully with haplo-SCT after induction therapy of alemtuzumab for T-PLL. Approximately 3 months after the achievement of complete remission with alemtuzumab for T-PLL, haplo-SCT with reduced-intensity conditioning and PTCy was performed. Infectious complications were improved by early therapeutic interventions, and peripheral T cell counts gradually

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recovered. The patient was alive for more than 16 months after allo-SCT with no signs of relapse. Thus, haplo-SCT using PTCy should be considered as an option after alemtuzumab treatment for T-PLL.

Introduction

T-cell prolymphocytic leukemia (T-PLL) is a rare aggressive T-cell leukemia with a median patient age of 65 years. It is refractory to conventional chemotherapy and has an aggressive clinical course with a median survival duration of patients of 1–2 years [1]. Intravenous alemtuzumab, a humanized CD52 antibody, induces remission in more than 80% of patients when used as first-line therapy. However, all patients eventually experience relapse after a short remission of 7–12 months, and many of them succumb to T-PLL [1].

Only allogeneic stem cell transplantation (allo-SCT) can provide long-term disease control in patients with T-PLL. Thus, the current recommended strategy is remission induction with alemtuzumab followed by consolidation with allo-SCT in eligible patients [1]. The most important hematologic adverse effect of alemtuzumab is a reduction in the count of lymphocytes including T and B cells and monocytes that express CD52, resulting in impaired cellular immunity [2]. Therefore, subsequent allo-SCT is associated with a higher risk of infections and an above-average transplant-related mortality (TRM) of 30–40% [1].

In the absence of human leukocyte antigen (HLA)-matched siblings and unrelated donors (MSD/MUD), grafts from HLA-haploidentical relatives are considered in allo-SCT because of their easy availability and widespread use. Post-transplant cyclophosphamide (PTCy) can suppress both graft-versus-host disease (GVHD) and graft rejection by depleting host and donor allogeneic reactive T cells in vivo. PTCy has become the most frequently used GVHD prophylaxis in haploidentical stem cell transplantation (haplo-SCT) because it is associated with lower NRM than other strategies such as ex vivo T-cell depletion [3]. As for T-PLL, only a retrospective study of 266 allo-SCT recipients has reported a 4-year overall survival rate of 33.9% and 4-year TRM rate of 31.6% in 30 patients who received haplo-SCT [4]. However, a limitation of this study was that details of pre-transplant induction therapy and post-transplant infections were not available and thus they were not included in the analysis. Therefore, the efficacy and tolerability of haplo-SCT with PTCy after induction therapy with alemtuzumab remain to be elucidated.

Here, we report an elderly patient with T-PLL who was treated successfully using haplo-SCT with PTCy after induction therapy with alemtuzumab. The CARE Checklist has been completed by the authors for this case report and attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000531471).

Case Report

A 66-year-old Japanese man with a history of early-stage bladder cancer and chronic obstructive pulmonary disease from past nicotine consumption was referred to our hospital for abdominal distension, and blood tests showed a marked increase in white blood cell count. Laboratory tests revealed a white blood cell count of 430,800/mL (95.5% of which were abnormal lymphocytes with round nuclei, visible nucleoli, and non-granular basophilic cytoplasm) (Fig. 1a). Flow cytometric analysis of peripheral blood lymphocytes demonstrated

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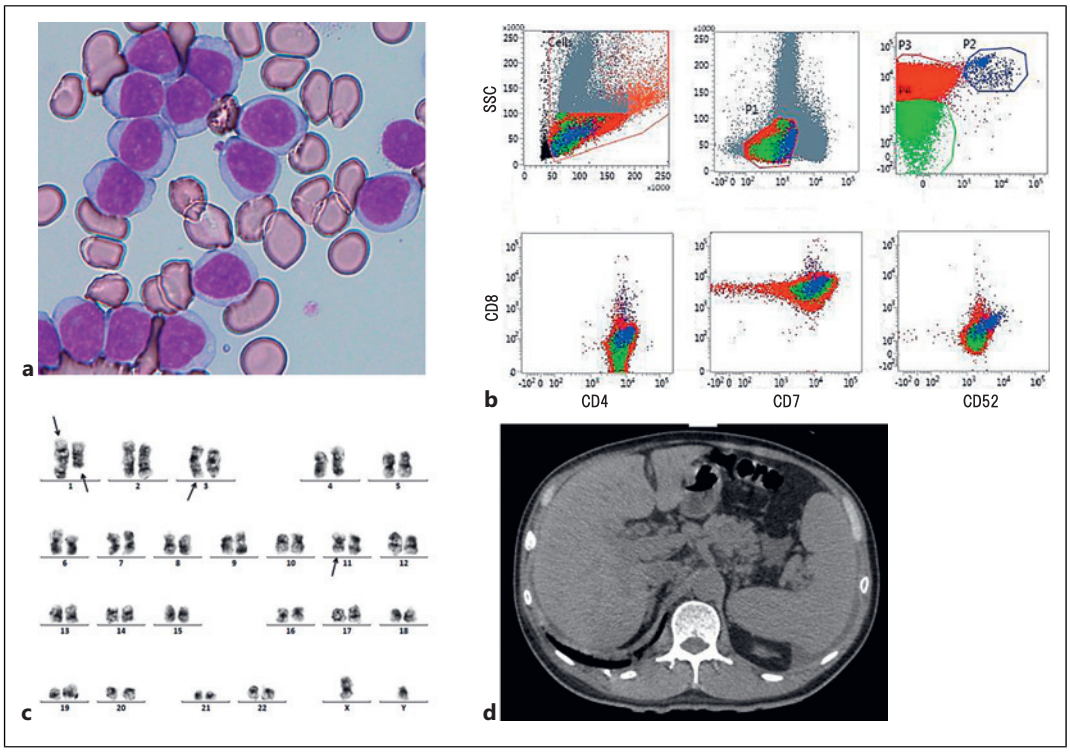

Fig. 1. Findings at diagnosis. **a** Bone marrow smear showed an increase in abnormal lymphocytes with round nuclei, visible nucleoli, and non-granular basophilic cytoplasm. **b** Flow cytometric analysis of peripheral blood detected abnormal T lymphocytes. The search for membrane CD3 (mCD3) and cytoplasmic CD3 (cyCD3) demonstrates that the major clones (red: 94.6%) display the aberrant mCD3(−), cyCD3(+) phenotype, whereas the minor clones (blue: 0.1%, green: 0.8%) display the mCD3(+), cyCD3(+) and mCD3(−), cyCD3(−) phenotype, respectively. **c** G-banding cytogenetic analysis of bone marrow aspirate showed complex karyotype with multiple chromosomal aberrations: 46,XY,add(1)(p11),?del(1)(q?),add(3)(q21),add(11)(q13),inc. **d** CT showed splenomegaly and lymphadenopathy.

an aberrant T-cell phenotype with post-thymic features, positive for CD2 and cytoplasmic CD3, CD4, CD5, CD7, CD45, CD52, and TCL1 and negative for membrane-associated CD3, CD8, CD19, CD20, CD25, CD34, CD56, CD79a, HLA-DR, and TdT (Fig. 1b). Polymerase chain reaction (PCR) analysis identified a clonal T-cell receptor β and γ chain gene rearrangement. Cytogenetic analysis detected a complex karyotype (Fig. 1c). Bone marrow examination showed 97.2% of mononuclear cells identical to peripheral blood. Computed tomography (CT) scanning revealed severe splenomegaly, systemic lymphadenopathy, and ascites (Fig. 1d). Thus, the patient was diagnosed with T-PLL.

A combination of fludarabine, mitoxantrone, and cyclophosphamide was administered as the first-line treatment because alemtuzumab is not approved for T-PLL in Japan. However, the treatment response after one course of fludarabine, mitoxantrone, and cyclophosphamide was a stable disease and considered refractory to conventional chemotherapy. Thereafter, intravenous alemtuzumab was started for off-label use as the second-line treatment. The dose administered was 3 mg on day 1, 10 mg on day 2, and 30 mg on days 3, 5, 8, 10, and 15. Pneumocystis, herpesvirus, and *Candida* prophylaxes were started after alemtuzumab administration. After starting alemtuzumab, leukocytosis was rapidly improved. No major complications were observed except for cytomegalovirus (CMV) reactivation, which was readily improved by valganciclovir administration. Follow-up CT scans showed resolution of

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lymphadenopathy and splenomegaly. Bone marrow and blood tests on day 23 revealed hematologic complete remission, but tumor cells persisted (0.013% in bone marrow and 0.086% in peripheral blood). Owing to minimal residual disease detection, the disease would relapse early and become life-threatening without allo-SCT as consolidation therapy.

As no HLA-matched donor was found for our patient, the patient's haploidentical daughter was considered as a donor. No donor-specific antibodies were detected. Anti-CMV antibodies were positive in both donor and recipient. The patient's hematopoietic cell transplantation-specific comorbidity index (HCT-CI) was 5 points (2 points for moderate pulmonary dysfunction and 3 points for prior solid tumor). Given the patient's advanced age, a high HCT-CI, a history of alemtuzumab administration, and the lack of an HLA-matched donor, the risk of NRM was considered very high. While allo-SCT could ensure long-term survival, it was also associated with a high relapse rate. We thoroughly informed about the risks and benefits of allo-SCT, after which the patient agreed to transplant. A reduced-intensity conditioning (RIC) regimen, consisting of fludarabine (30 mg/m^2 on days 7 to 2), melphalan (40 mg/m^2 on days 3 and 2), and total body irradiation (TBI, 2 Gy on day 1), was used. GVHD prophylaxis comprised PTCy (40 mg/kg on days 3 and 4), tacrolimus (initiated at a dose of 0.02 mg/kg from day 5), and mycophenolate mofetil (initiated at a dose of 30 mg/kg from day 5 and stopped on day 48) (Fig. 2). A peripheral blood graft with 2.79 × 10^6 CD34-positive cells/kg was infused on day 0. The time interval from the last dose of alemtuzumab to allo-SCT was 85 days.

On day 4, the patient developed febrile neutropenia and required antibiotics. A high fever recurred on day 3, which resolved after PTCy administration on days 3 and 4. *Corynebacterium striatum* bacteremia resulting from a catheter-related bloodstream infection occurred on day 10, and vancomycin was administered until day 27. Neutrophil engraftment was achieved on day 18. Bone marrow examination on day 29 showed complete donor chimerism, and no tumor cells were detected by flow cytometric. The patient had prolonged fever after engraftment, and on day 35, multiple small nodule lung shadows appeared on a CT scan. The results of serological analysis, including beta-D glucan and *Aspergillus* galactomannan analysis, and bacterial and fungal cultures of blood and bronchoalveolar lavage (BAL) fluid were negative. Furthermore, analysis results for viral infection, including CMV antigen and comprehensive genetic testing, were negative. From these findings, bacterial, fungal, and viral infections were ruled out. Drug-induced pneumonia and GVHD were inconsistent with the clinical course and physical findings. Considering that, tuberculosis (TB) is not rare among elderly individuals in Japan and that the lung shadow was suggestive of TB, we strongly suspected miliary TB. Therefore, anti-TB drugs were initiated, and a rifampicin-sparing regimen (isoniazid, ethambutol, pyrazinamide, and levofloxacin) was selected because rifampicin strongly interacts with immunosuppressive agents, such as calcineurin inhibitors, mycophenolate mofetil, and azole antifungals, and increases the risk of hepatotoxicity [5]. The results of mycobacterial culture and PCR of the patient's sputum, gastric aspirates, BAL, transbronchial biopsy, blood, bone marrow, stool, and urine were negative. However, after the initiation of anti-TB drugs, the fever resolved, the lung shadow disappeared, and treatment-related adverse events were minimal. Therefore, as discussed below, we considered the results as false negative and decided to continue treatment for TB.

After transplantation, CMV antigenemia was monitored regularly, and prophylaxis with letermovir was administered. After the completion of prophylaxis on day 100, CMV reactivation was observed on day 111, but it rapidly improved with valganciclovir administration. On day 73, cutaneous eruptions appeared and gradually spread to the trunk and extremities. On day 111, a skin biopsy was performed, which suggested acute GVHD (skin: stage 3; gut and liver: none). Systemic corticosteroid therapy (prednisolone 0.5 mg/kg) was administered, and the eruptions improved rapidly and disappeared by day 120. Tacrolimus and prednisolone

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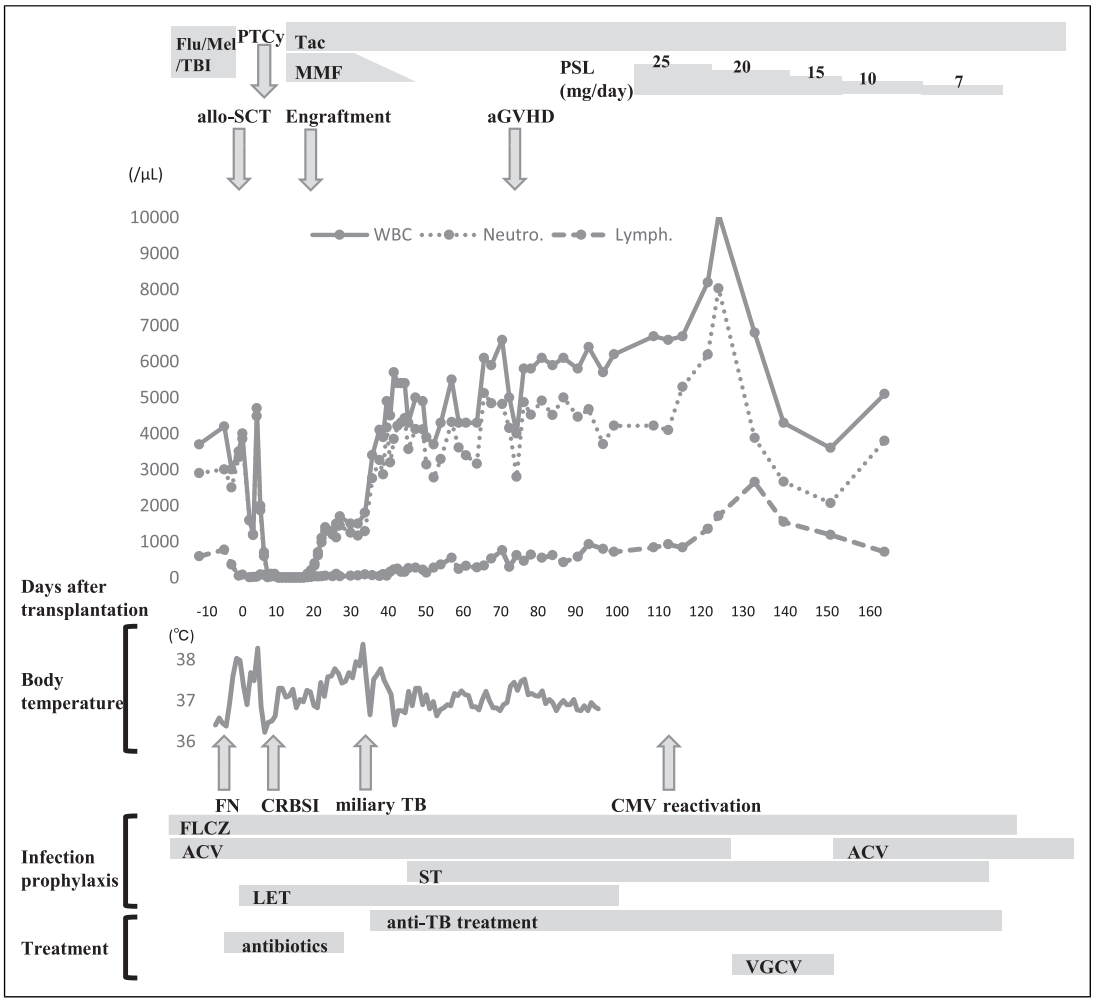

Fig. 2. Clinical course after transplantation. Changes in the number of peripheral white blood cells (WBC), neutrophils, and lymphocytes, as well as changes in body temperature during hospitalization, are shown. Flu, fludarabine; Mel, melphalan; Tac, tacrolimus; MMF, mycophenolate mofetil; PSL, prednisolone; aGVHD, acute graft-versus-host disease; FN, febrile neutropenia; CRBSI, catheter-related bloodstream infection; TB, tuberculosis; CMV, cytomegalovirus; FLCZ, fluconazole; ACV, acyclovir; ST, sulfamethoxazole and trimethoprim; LET letermovir, VGCV, valganciclovir.

doses were gradually tapered from day 127, and skin GVHD still required small doses of immunosuppressive drugs, but there had been no GVHD flare-ups. As shown in Table 1, the peripheral T lymphocyte fraction was low immediately before transplantation, persisting until post-engraftment but gradually returned to the normal range after day 111. More than 16 months after allo-SCT, the patient has shown a good performance status with no signs of relapse and complete donor chimerism.

Discussion

We treated a patient using RIC haplo-SCT with PTCy after remission induced with alemtuzumab for T-PLL. Allo-SCT is an effective treatment for T-PLL and can induce durable remission. Nevertheless, allo-SCT for T-PLL is associated with high rates of early relapse

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Table 1. T-lymphocyte fraction of peripheral blood

Day from transplant	−78	−15	35	111	160
WBC, /μL	1,200	3,700	4,100	6,700	3,600
Lymphocyte, /μL	78	592	41	838	1,188
T cell ($CD3^+$), /μL	69	78	36	644	848
$CD4^+$T cell, /μL	4	22	13	164	207
$CD8^+$T cell, /μL	64	55	19	473	623
$CD4^+/CD8^+$	0.1	0.4	0.7	0.3	0.3

WBC, white blood cells.

(30–40%) and considerably high rates of TRM (30–40%), which challenge patients' post-SCT survival chances [1]. As alemtuzumab causes severe lymphocytopenia, subsequent allo-SCT can lead to more severe cellular immunodeficiency and increase the risk of life-threatening viral, bacterial/mycobacterial, and fungal infections. In addition, in cases lacking HLA-matched donors, alternative donors such as HLA-haploidentical donors, mismatched unrelated donors (MMUDs), or unrelated cord blood (UCB) donors must be found; however, there are only a few reports on transplantation using alternative donors for T-PLL.

Haplo-SCT using PTCy is being increasingly used, and the results are comparable to allo-SCT with MSDs, MUDs, and UCB donors [3]. To clarify infectious complications in haplo-SCT with PTCy, Irene et al. compared severe infections in patients treated with allo-SCT from haploidentical donors and MSDs/MUDs/MMUDs [6]. Pre-engraftment bloodstream infections and invasive fungal infections did not differ between haplo-SCT and non-haplo-SCT (45% vs. 40.5% and 7.5% vs. 9%, respectively). Regarding viral infections, the incidence of CMV infection/reactivation and viral hemorrhagic cystitis was significantly higher in the haplo-SCT group than in the non-haplo-SCT group (58% vs. 43% and 30% vs. 8%, respectively). However, donor type had no effect on infection-related mortality (18-month infection-related mortality: 7.9% in haplo-SCT vs. 13.4% in non-haplo-SCT). For T-PLL, Murthy et al. reported the outcomes of patients treated using allo-SCT with MSDs, MUDs, haploidentical donors, and MMUDs, and showed that, although the number of patients was small and detailed data such as those pertaining to infection were lacking, disease-free survival, and overall survival in haplo-SCT were comparable to MUD and MMUD transplants. Moreover, PTCy-based GVHD prophylaxis was associated with less chronic GVHD than calcineurin inhibitor-based GVHD prophylaxis [4]. As for UCB transplants, three cases have been reported; 1 patient reportedly died of fatal adenovirus encephalomyeloradiculitis [7–9]. Compared to haplo-SCT with PTCy, UCB transplantation is associated with slow hematopoietic recovery and high rates of NRM, including infection-related mortality [3]. Based on these findings, we selected a haploidentical-related donor as the transplant source for the patient.

As there is no consensus on the time between the last dose of alemtuzumab and transplantation, the optimal timing of transplantation should be determined in each case. Although the risk of disease progression before transplantation must be considered, a washout period is desirable to eliminate the immunosuppressive effects of alemtuzumab, which may damage the graft and impede graft-versus-host activity [1]. The average plasma half-life of alemtuzumab is 7–8 days, but it takes approximately 2 months for alemtuzumab concentration to drop below 0.1 μg/mL. As alemtuzumab opsonizes lymphocytes at concentrations as low as 0.1 μg/mL and exhibits antibody-dependent cellular cytotoxicity, it is likely that lymphocyte clearance continues even after 2 months [2]. Based on these findings, the time interval was set to 3 months in this case. The lymphocyte counts were able to recover to the normal range around 100 days after transplantation, which is consistent with the

already known course of conventional T-cell reconstitution after haplo-SCT using PTCy [10]. Optimal conditioning intensity of allo-SCT for T-PLL is also a matter of debate. TBI of 6 Gy or higher has been reported to have a lower risk of relapse [1], whereas myeloablative conditioning is associated with increased TRM [4]. Although our patient had a complex karyotype associated with poorer overall survival than the normal karyotype [11], RIC was selected because of his advanced age and high HCT-CI, TBI was limited to 2 Gy because of chronic obstructive pulmonary disease, and the dose of PTCy was reduced to 80 mg/kg [12]. Consequently, engraftment was achieved, GVHD was controllable, and the patient's disease has been under control. Further studies are needed to determine whether transplantation for T-PLL with complex karyotypes has a prognostic value.

Definitive diagnosis of TB in immunocompromised patients, such as those infected with HIV or after hematopoietic stem cell transplantation, is usually difficult because immunodeficiency results in a diminished inflammatory response and false-negative results [5]. There have been several reports on culture test sensitivity in HIV-infected patients with TB. Worodria et al. reported the results of sputum cultures and BAL smears and cultures in 107 HIV-infected patients with suspected TB and negative sputum smears. Of the 39 patients with the diagnosis of pulmonary TB, 13 patients (33%) were negative for both sputum culture and BAL smear/culture and were diagnosed with TB based solely on their clinical response to treatment [13]. Chemeda et al. [14] reported on the efficacy of urine analyses in the diagnosis of TB in 117 HIV-positive patients with suspected pulmonary TB. The sensitivity of urine culture was only 39.4%, whereas the sensitivity of PCR of urine increased to 72.7%. Nakiyingi et al. [15] also reported a positive rate of 23% in sputum and/or blood cultures for TB of 418 sputum smear negative patients with HIV infection and suspected active TB. It is challenging to detect TB in these immunocompromised patients using culture studies, and high-resolution CT scan has been reported to have 90% sensitivity of pulmonary TB in febrile neutropenia [5]. Our patient was suspected to have miliary TB from the CT findings, and the patient's general condition improved after the immediate administration of anti-TB drugs. The decreased peripheral T-cell fraction even after engraftment suggested that severe cellular immunodeficiency persisted, which may contribute to the reactivation of latent TB. Although the culture test results were negative, we continued TB treatment considering the high mortality rate in the event of TB in the immunocompromised state after allo-SCT [5]. Isoniazid prophylaxis based on interferon-gamma release assay (IGRA) results has been reported to be effective in allo-SCT recipients, although routine prophylaxis is not recommended because of hepatotoxicity [5]. In our patient, isoniazid prophylaxis should have been considered based on pretreatment IGRA result and TB risk assessment because of the increased risk of TB in allo-SCT such as alemtuzumab and cyclophosphamide [5].

Conclusion

T-PLL has a poor prognosis, and allo-SCT following alemtuzumab is currently the most promising treatment that can provide long-term survival, whereas high TRM because of the persistence of a highly immunosuppressed state poses concerns. Furthermore, only a few studies have reported transplants using alternative donors, but the outcomes are still unclear. In this case, haplo-SCT using PTCy was safely performed after achieving complete remission with alemtuzumab induction for T-PLL. Post-transplant T-cell reconstitution was successfully achieved with the interval from the last dose of alemtuzumab to transplantation. Although further validation in a large number of patients is needed, haplo-SCT with PTCy could be a tolerable and effective therapeutic option for T-PLL.

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Statement of Ethics

This case report was approved by the clinical ethics committee of Kobe City Medical Center General Hospital (approval number 22178). The off-label use of alemtuzumab administration for T-PLL was approved by the Committee for Appropriate Use of Drugs and Medical Devices of Kobe City Medical Center General Hospital. The patient provided written informed consent for the publication of this case report and accompanying images.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest to declare.

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Author Contributions

N.O. and R.Y. wrote the manuscript. H.M. and M.H. analyzed the data and helped in writing the figure. N.H. and T.I. revised the manuscript. T.I. supervised the case. All authors approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in the case report. Further inquiries can be directed to the corresponding author.

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