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【 CASE REPORT 】

Successful Bridging Chemotherapy with Gemcitabine, Carboplatin, and Dexamethasone before Unrelated Stem Cell Transplantation for Hepatosplenic T-cell Lymphoma

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Abstract:

A 45-year-old woman was diagnosed with hepatosplenic T-cell lymphoma (HSTCL), a rare subtype of peripheral T-cell lymphoma. She received different types of chemotherapy, but disease progression was observed. To reduce the tumor burden before an unrelated bone marrow transplantation, combination chemotherapy consisting of the gemcitabine, carboplatin, and dexamethasone (GCD) was administered as bridging therapy, resulting in a reduction in the number of lymphoma cells. We were then able to perform bone marrow transplantation. Although she experienced some adverse events, she successfully achieved long-term remission. We herein report a successful case of HSTCL treated with unrelated stem cell transplantation following the GCD regimen as bridging chemotherapy.

Key words: hepatosplenic T-cell lymphoma, GCD, allogeneic stem cell transplantation, bridging therapy

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Introduction

Hepatosplenic T-cell lymphoma (HSTCL) is a very rare subtype of peripheral T-cell lymphoma. Mainly seen in young men with a median age of 34 years, HSTCL accounts for 3% of all T-cell lymphomas in North America, 2.3% in Europe, and only 0.2% in Asian countries, making it rare in the Japanese population (1). However, the incidence of HSTCL has recently been increasing (2). HSTCL also occurs in patients with immunodeficiency, potentially caused by chronic immunosuppressive therapy after solid-organ transplantation or by collagen or inflammatory bowel disease (3). HSTCL is characterized by a fever, fatigue, weight loss, night sweats, hepatosplenomegaly, and pancytopenia without lymphadenopathy (4).

HSTCL has an aggressive clinical course, with a poor prognosis and a 5-year survival of only 7% (1) or 14.6% (2) in large-cohort studies. There is no standard regimen for HSTCL treatment, and HSTCL is refractory and relapses quickly (4). Therefore, allogeneic hematopoietic stem cell transplantation (HSCT) is needed for the treatment of incurable lymphoma, thereby resulting in long-term remission in as many as 40% of patients (5). It is very important to control the underlying disease and the patient's general condition before HSCT in order to determine the best timing for HSCT, as the date of HSCT from unrelated donors is decided mainly according to the convenience and schedule of

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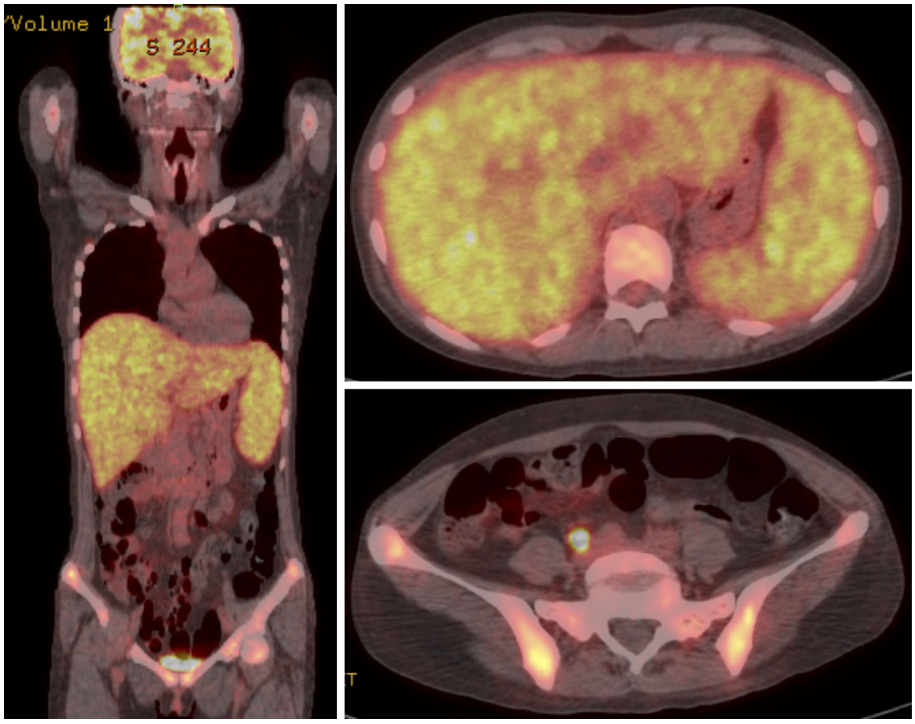

Figure 1. **A positron emission tomography-computed tomography scan showing hepatosplenomegaly and abnormal fluorodeoxyglucose accumulation in the liver, spleen, and bones without systemic lymphadenopathy.**

the donor, the hospital where the stem cells are harvested, and, to some degree, the recipient.

We herein report a case of HSTCL successfully treated with bridging chemotherapy consisting of gemcitabine, carboplatin, and dexamethasone (GCD) (6) before unrelated allogeneic HSCT.

Case Report

A 45-year-old woman had a fever and fatigue for a month before she visited another clinic, where thrombocytopenia was detected. Thereafter, she was referred to a general hospital for detailed examinations. A physical examination revealed a fever, along with hepatomegaly and splenomegaly but no lymphadenopathy. She had no remarkable medical history.

Laboratory studies revealed elevated levels of aspartate aminotransferase (106 U/L), alanine aminotransferase (73 U/L), alkaline phosphatase (745 U/L), lactate dehydrogenase (LDH, 1,982 U/L), and soluble interleukin-2 receptor (sIL-2R, 6,370 U/L). Anti-human T-cell lymphotropic virus type 1 antibody was negative, and the results of serological tests for Epstein-Barr virus indicated a previous infection. Whole-body positron emission tomography-computed tomography (PET-CT) revealed hepatosplenomegaly with no focal lesions, but the abnormal accumulation of fluorodeoxyglucose (FDG) was observed in the liver, spleen, and bones (Fig. 1).

Bone marrow aspiration resulted in a dry tap, and bone marrow biopsy showed hypertrophy, along with medium-sized abnormal lymphocytes. These lymphocytes were positive for CD3 and T-cell-restricted intracellular antigen (TIA-1) and negative for CD4, CD8, and granzyme B as well as for Epstein-Barr virus-encoded RNA on *in situ* hybridization (EBER-ISH). The abnormal lymphocytes from the bone marrow showed a monoclonal gene rearrangement of the TCR-γ chain, and the karyotype was 48, XX, +mar 2 [6/6].

Because the patient had hepatomegaly and abnormal liver enzyme levels, a liver biopsy was also performed, which revealed diffuse sinusoidal dilation containing the same abnormal lymphocytes that were positive for CD3, CD56, TCR-γδ, and TIA-1 but negative for CD20, CD4, CD8, TCR-αβ, and EBER-ISH (Fig. 2). Based on these findings, the patient was diagnosed with HSTCL.

Because the prognosis of HSTCL patients is known to be poor and the patient was young without any organ failure, her previous doctors selected ESHAP, which has a more-intensive induction regimen than CHOP, as the initial chemotherapy regimen. She received four cycles of the ESHAP regimen (etoposide 40 mg/m^2/day for 4 days, methylprednisolone 500 mg daily for 5 days, cisplatin 25 mg/m^2 for 4 days, and cytarabine 2 g/m^2 intravenously on day 5). The patient was then referred to our hospital to undergo allogeneic HSCT. However, even after four cycles of ESHAP, her bone marrow examination showed that abnormal lymphocytes still existed at a proportion of approximately 4.4%.

Therefore, to prepare the patient for unrelated HSCT, we administered salvage chemotherapy with the hyper-CVAD regimen (6 doses of cyclophosphamide 300 mg/m^2 over 3 hours every 12 hours on days 1 through 3, with mesna at

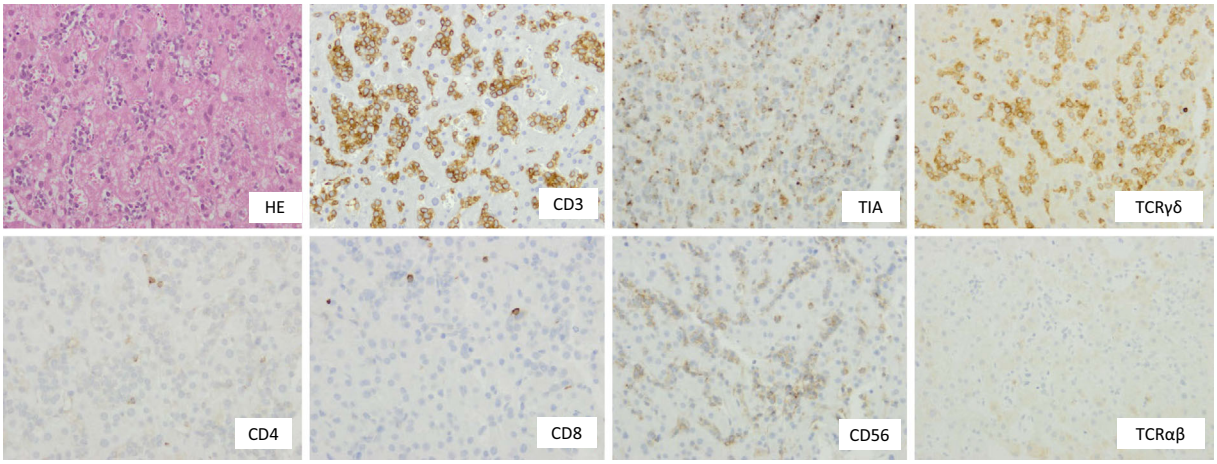

Figure 2. **Histopathological findings. The liver biopsy showed many abnormal lymphocytes, infiltrating the hepatic sinusoid. These cells were positive for CD3, CD56, TCR-γδ, and TIA-1 but negative for CD4, CD8, TCR-αβ, and EBER-ISH (20× objective). EBER-ISH: Epstein-Barr virus-encoded RNA on *in situ* hybridization**

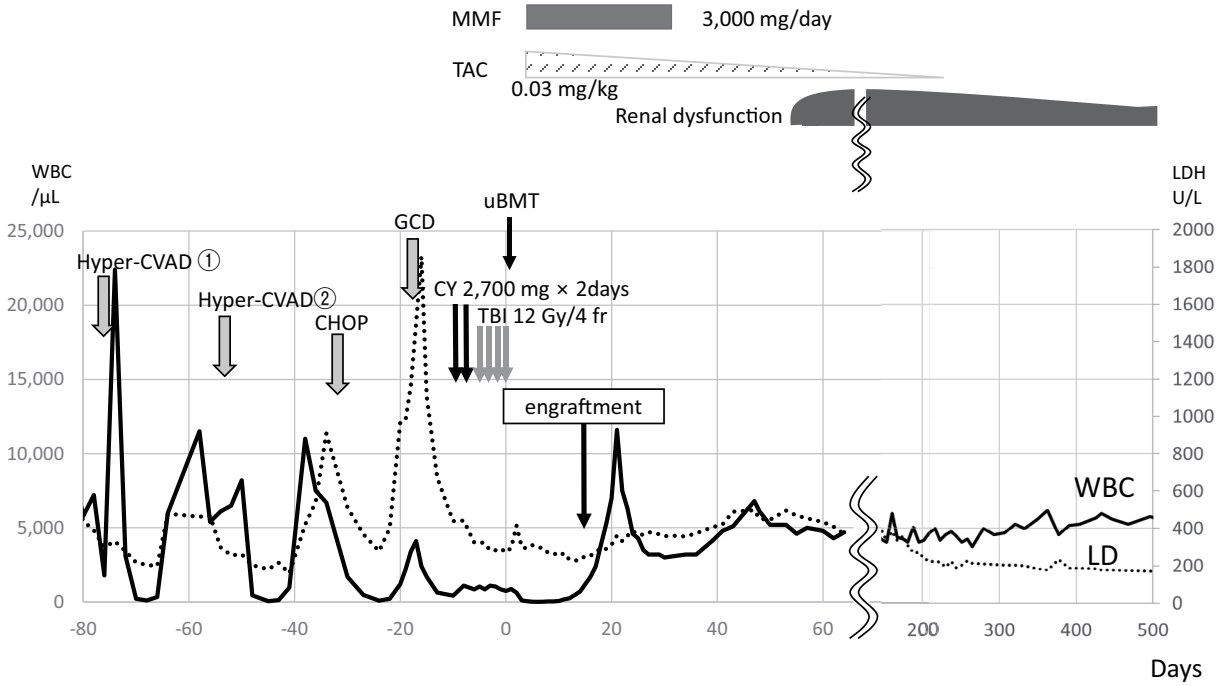

Figure 3. **The clinical course of the patient. MMF: mycophenolate mofetil, TAC: tacrolimus, CY: cyclophosphamide, TBI: total-body irradiation**

the same total dose as cyclophosphamide but administered via continuous infusion starting with cyclophosphamide and ending 6 hours after the last dose; vincristine 2 mg on days 4 and 11; doxorubicin 50 mg/m^2 on day 4; and dexamethasone 40 mg daily on days 1 through 4 and 11 through 14). Although two cycles of the hyper-CVAD regimen were administered, the patient presented with an elevated lymphocyte count and elevated LDH levels, indicative of progressive disease. Bone marrow aspiration revealed an abnormal lymphocyte proportion of 54.6%.

As there were only 20 days left until the scheduled date for unrelated HSCT, in order to reduce her tumor burden before HSCT, we started chemotherapy with the CHOP regimen (cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, and vincristine 1.4 mg/m^2, administered intravenously on day 1, and oral prednisone 100 mg on days 1 through 5). However, the LDH level was still elevated, and abnormal lymphocytes were detected in the peripheral blood (Fig. 3), with no change in the FDG accumulation pattern in the liver or spleen on PET-CT. Therefore, the day of HSCT was postponed to two weeks after the initially scheduled day of HSCT.

In order to reduce the abnormal lymphocyte count as much as possible before transplantation, we administered bridging chemotherapy consisting of GCD (gemcitabine; 1,000 mg/m^2, on days 1 and 8; carboplatin, AUC=5, on day

1; and dexamethasone, 33 mg, on days 1 to 4) to prepare for HSCT. The leukocyte counts and LDH levels decreased after the GCD regimen, and no abnormal lymphocytes were observed in the peripheral blood. Although the bone marrow did not fully recover (white blood cell count of 1,040/μL, hemoglobin level of 7.1 g/dL, and platelet count of 26,000/μL) by day 13 of the GCD regimen, the patient's general condition improved, and we decided to start administering the myeloablative conditioning regimen consisting of cyclophosphamide (60 mg/kg for 2 days) and total-body irradiation (12 Gy/4 fr). Tacrolimus and mycophenolate mofetil (MMF) were used for graft-versus-host disease (GVHD) prophylaxis, and ursodeoxycholic acid was used for prophylaxis of sinusoidal obstruction syndrome. On day 4 of the conditioning regimen, the patient developed transient hemorrhagic cystitis caused by the BK virus. Neutrophil engraftment was achieved on day 14 after HSCT. MMF was discontinued on day 30 without tapering in order to induce the graft-versus-lymphoma effect.

One month after transplantation, the patient started to complain of nausea and vomiting; acute gut GVHD was suspected. Although gastroendoscopy revealed mucous redness, a gastric biopsy only revealed non-specific inflammation with no findings indicative of GVHD. Gastroscopy was repeatedly performed, which also revealed diffuse mucosal edema and redness without findings of acute GVHD.

The gastrointestinal symptoms had been gradually ameliorating and vanished at approximately one year after HSCT. However, her renal function deteriorated gradually, and the highest serum creatinine level was 2.89 mg/dL at approximately day 100 after transplantation. After the peak, the serum creatinine level decreased and remained at 2 mg/dL [estimated glomerular filtration rate (eGFR): approximately 20 mL/min/1.73 m^2].

The patient underwent rehabilitation and was discharged on day 129. A bone marrow examination and PET-CT performed after approximately one year revealed complete remission. Although the serum creatinine level was still approximately 2 mg/dL, the patient's overall condition was good without any symptoms.

Discussion

We successfully treated a case of HSTCL via timely treatment with the GCD regimen for disease control prior to the conditioning regimen for HSCT. For unrelated HSCT, only donors-not patients - can decide the date of HSCT. Therefore, it is very important to control the underlying disease and the patients' general condition before HSCT in order to achieve the best timing of HSCT. The CHOP regimen is often used as bridging therapy for HSCT in patients with lymphoid malignancies because of the limited toxicity associated with this regimen. In our case, we initially used the CHOP regimen as bridging chemotherapy just before transplantation. Although there are a few differences between hyper-CVAD and CHOP, we selected CHOP for the following reasons: (1) hyper-CVAD still has certain effects for cytoreduction, (2) CHOP is less toxic than hyper-CVAD, and (3) CHOP is often used as bridging chemotherapy in our hospital to reduce the tumor burden in patients with lymphoid malignancies. We prioritized the reduction of tumor cells over achieving complete remission, to safely perform transplantation, since we expected the graft-versus-lymphoma effect. Unfortunately, the cytoreductive effect of the CHOP regimen only lasted for a short period, and the LDH increased before bone marrow recovery, as presented in Fig. 1. We needed to perform additional bridging therapy, so we adopted the GCD regimen for disease control before HSCT.

The diagnosis of HSTCL is difficult because the symptoms of HSTCL are not clinically specific, which can easily result in a misdiagnosis, such as the flu or liver disease (4, 7, 8). In the present case, the patient presented with hepatosplenomegaly, a low-grade fever, thrombocytopenia, anemia, and liver dysfunction with abnormal lymphocytes in the peripheral blood without systemic lymphadenopathy. Although these symptoms supported the diagnosis of HSTCL, an appropriate diagnosis was difficult, as flu was suspected initially. Immunophenotypic analyses performed via a histopathological approach or flow cytometry play a definitive role in the diagnosis of HSTCL (3, 4). Lymphoma cells of HSTCL are usually positive for CD2, CD3, CD38, and CD56 and negative for CD4, CD5, and CD8. In our case, lymphoma cells infiltrating the bone marrow were positive for CD3, CD56, and TIA-1 and negative for CD4, CD8, and EBER-ISH (4). As mentioned above, our patient was definitively diagnosed with HSTCL.

While up to 50% of patients may achieve complete remission with chemotherapy, remissions are typically short-lived, and the median overall survival is only approximately 1 year (4). Delaying the treatment of HSTCL due to difficulties in confirming the diagnosis may lead to a poor prognosis. Although data on the treatment of HSTCL are limited, the outcome of chemotherapy alone seems to be poor. Furthermore, there are no established standard treatments owing to its low prevalence, thereby resulting in the inability to perform large-scale clinical trials. Belhadj et al. reported a case series of 21 patients with HSTCL (7). Nineteen of the 21 patients received CHOP or a CHOP-like regimen, and the remaining 2 received a platinum-cytarabine-based regimen with or without splenectomy as the first-line treatment. Nine out of the 19 patients treated with CHOP or a CHOP-like regimen achieved complete remission, 3 achieved partial remission, and 7 experienced treatment failure. The two patients treated with the platinum-cytarabine-based regimen achieved partial remission. However, despite a good response to initial chemotherapy, relapse occurred early. The median survival was reported to be 16 months, and only 2 patients who underwent autologous PBSCT were alive (42 and 52 months from the diagnosis of HSTCL) at the time of the analysis (7). Falchook et al. reported another case series of 15 HSTCL patients (8). Nine out of 15 patients were in-

itially treated with CHOP or a CHOP-like regimen; 5 patients achieved complete remission, and 1 patient achieved partial remission. Only the two patients who did not receive CHOP or a CHOP-like regimen achieved complete remission; 1 patient received platinum-cytarabine-based regimen, and the other received pentostatin and alemtuzumab therapy. Patients who achieved complete remission had a median survival of 13 months compared to 7.5 months in patients who did not achieve complete remission. All four long-term survivors achieved complete response after initial chemotherapy; two received allogeneic HSCT, one received autologous HSCT, and the other did not receive HSCT.

Durani et al. reported that the median overall survival of patients who did and did not receive HSCT was 34.4 and 6.7 months, respectively (2). Rashidi et al. conducted a systematic review of allogeneic SCT including 54 eligible HSTCL cases and found that as many as 40% of patients with HSTCL who underwent allogeneic SCT experienced long-term remission (5). The remission status before HSCT had no significant impact on the relapse-free or overall survival (5, 9); however, it tended to yield a good overall survival (hazard ratio=0.56, 95% confidence interval: 0.18-1.79, p=0.33), suggesting the potency of the graft-versus-lymphoma effect. Therefore, we attempted to reduce the tumor burden by performing chemotherapy before HSCT. In this case, since we were unable to inhibit the tumor growth with the CHOP regimen, we used the GCD regimen as additional bridging chemotherapy.

Gemcitabine inhibits the transition from the G1 phase to the S phase during cell proliferation (10). It proved to be effective in relapse/refractory peripheral T-cell lymphoma as a single agent or in combination with other conventional antitumor drugs. The overall response rates of monotherapy of gemcitabine and the gemcitabine-based combination regimen were 51% and 88.5%, respectively (11, 12). However, these reports included peripheral T-cell lymphoma, not otherwise specified; mycosis fungoides; and anaplastic large-cell lymphoma but not HSTCL.

Although many kinds of drugs have been administered in combination with gemcitabine, especially the GCD regimen, combination treatment with gemcitabine, carboplatin and dexamethasone, has also been reported to be effective and is associated with fewer adverse events and therefore it can even be administered to outpatients. A previous report in 51 patients administered the GCD regimen found that adverse events of grade 3 and 4 hematologic toxicities occurred in 22% and 39% of patients, respectively; however, there were no cases of life-threatening bleeding, infectious complications, or treatment-related deaths. Febrile neutropenia and grade 4 non-hematologic toxicities were rare. The most common (>10%) non-hematologic adverse events of grade 3 or higher were laboratory abnormalities (22%), cardiovascular events (14%), and pain (12%). Grade 3 cardiovascular adverse events included central catheter-associated thrombosis, hypotension, and a vasovagal episode after the removal of an apheresis catheter (6). We speculate that the GCD regimen is one of the treatment options available as bridging therapy for HSCT to reduce the tumor burden of lymphoma without severe adverse events.

The clinical course of the current patient was eventful. She experienced long-term hypophagia, gastritis, and renal failure. No pathological signs of acute GVHD or cytomegalovirus infection were observed even on repeated gastroendoscopy, although these symptoms might have been caused by the conditioning regimen or prior chemotherapy, including the GCD regimen. Regarding renal dysfunction, the eGFR had been maintained at approximately 20 mL/min/1.73 m^2 without dialysis for more than 1 year after HSCT. Our patient transiently required hydration during tacrolimus treatment to maintain her renal function even after discharge. However, long-term remission was achieved with the GCD regimen to reduce tumor burden and ensure the timely performance of allogeneic HSCT.

In conclusion, we encountered a successful case of HSTCL treated with the GCD regimen for disease control before the conditioning regimen for HSCT. The GCD regimen might be one of the few treatment options that can be performed sequentially before myeloablative conditioning regimens as bridging therapy for refractory HSTCL.

The authors state that they have no Conflict of Interest (COI).

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