Effect of chidamide on treating hepatosplenic T-cell lymphoma: A case report

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Abstract

BACKGROUND
Hepatosplenic T-cell lymphoma (HSTCL) is a rare subtype of non-Hodgkin’s lymphoma, which has an aggressive clinical course and an extremely poor prognosis. Chidamide is a novel, orally active, benzamide-type histone deacetylase (HDAC) inhibitor that has been used for peripheral T-cell lymphoma (PTCL) treatment. However, to date, there has been no report of the treatment and effect of the HDAC inhibitor chidamide in HSTCL, which is a special subtype of PTCL.

CASE SUMMARY
A 45-year-old male patient was admitted with splenomegaly and slight cytopenia. He was diagnosed with HSTCL via splenectomy. The patient was treated with fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine regimen as inductive therapy. Unfortunately, the disease progressed rapidly during chemotherapy before a suitable allogeneic bone marrow donor was found. The chidamide-combined chemotherapy regimen and single-drug oral maintenance regimen achieved complete remission, duration of response of 9 mo, and overall survival of 15 mo.

CONCLUSION
The novel agent chidamide can be used in HSTCL to achieve deep remission and
INTRODUCTION

Hepatosplenic T-cell lymphoma (HSTCL) is a rare and aggressive subtype of peripheral T-cell lymphoma (PTCL)\(^9\). This tumor mostly arises from the gamma-delta (γδ) T cells and predominantly affects middle-aged males\(^9\). Since this is a rare disease, the mechanism has not been well elucidated. Persistent antigen stimulation and immunosuppressive therapy are two possible factors for the development of this disease\(^9,10\). Unlike other nodal T-cell lymphomas, this disease has no lymphadenopathy, but main manifestations include marked splenomegaly, hepatomegaly, and pancytopenia with bone marrow involvement\(^4\). The diagnosis of HSTCL is usually based on core needle biopsies of the liver or bone marrow; however, patients presenting primarily with splenic enlargement may be diagnosed with splenectomy instead. A prominent sinusoidal infiltrate of medium-sized lymphoid cells with the characteristic immunophenotype (CD2+/CD3+, CD4−/CD8−, CD5−, restricted γ/δ T-cell receptor TCR\(^1\) in the liver, spleen, and/or bone marrow is sufficient for the diagnosis of HSTCL with corresponding clinical manifestations\(^11\). Isochromosome 7q in cytogenetics strongly supports the diagnosis of HSTCL if identified\(^11\). HSTCL is refractory to chemotherapy with unremitting clinical progression, which leads to an extremely low 5-year overall survival (OS, < 10%)\(^7\) and a quite short median survival (12-14 mo)\(^8\). The treatment for HSTCLs is still challenging even with high-dose chemotherapy and stem cell transplantation (SCT). Chidamide (CS055/HBI-8000) is an oral histone deacetylase (HDAC) inhibitor that has been prescribed in China for the treatment of relapsed and recurrent PTCL\(^9\). Chidamide monotherapy showed a good overall response rate (39.06%), and disease control rate (64.45%) in PTCL treatment. Combination with chemotherapy proved longer median progression-free survival (152 d vs 129 d [monotherapy], \(P = 0.33\))\(^8\). There are still no data on the effect of chidamide on HSTCL.

Here, we report a first of its kind treatment with the HDAC inhibitor chidamide, achieving a satisfactory outcome in an HSTCL patient who showed rapid progress with traditional chemotherapy.

CASE PRESENTATION

Chief complaints

A 45-year-old male patient presented with a 2-mo history of abdominal pain and fatigue, and he was admitted to The First Hospital of Jilin University (Changchun, Jilin, China).
History of present illness
The patient’s symptoms started 2 mo prior when he began a daily fitness routine. There was pain and persistent bloating in the abdomen with fatigue that aggravated slowly until he was referred to the hospital. He had no symptoms of fever or night sweats. Weight loss recorded in the last 5 mo was approximately 5 kg.

History of past illness
The patient had no previous history of immune system disease or immunosuppressive drug use.

Personal and family history
The patient had no family history of malignant tumors or blood system diseases.

Physical examination upon admission
Physical examination revealed mild epigastric abdominal tenderness and splenomegaly 7 cm below the costal margin without hepatomegaly or peripheral lymphadenopathy.

Laboratory examinations
Laboratory tests showed white blood cell count of 5.05 × 10^9/L, with a prominent absolute lymphocyte count of 2.47 × 10^9/L, hemoglobin 9.8 g/dL, and platelet count 109 × 10^9/L. The lactate dehydrogenase was 205.1 U/L, erythrocyte sedimentation rate 12 mm/h, and β2-microglobulin 6.72 mg/L. Liver function and renal function tests were normal. The viral markers (hepatitis B, hepatitis C, and human immunodeficiency viruses), tumor markers (alpha-fetoprotein, carcinoembryonic antigen, and cancer antigen-199), infection profile (Breitbart), and autoimmune profile (antinuclear antibodies and antineutrophil cytoplasmic antibody) were unremarkable.

Imaging examinations
Fluorodeoxyglucose (FDG)-positron emission computed tomography (PET-CT) scan showed significant spleen enlargement with mildly increased FDG uptake (SUV 3.1) and mild liver enlargement (Figure 1A). Histopathology from the splenectomy showed that the tumor tested positive for CD2, surface CD3, CD4, and CD 56 and negative for CD8 and B-cell markers (CD20 and CD79a). The cytotoxic granule protein TIA-1 was expressed, but perforin and granzyme B scatter were positive (Figure 2A-E). In situ hybridization of the Epstein–Barr virus genome showed no abnormality (Figure 2F). Molecular pathology showed positive TCR-γδ rearrangement (Figure 2C), while TCR-αβ was negative. Ki-67 was positive in 70% of atypical cells. Bone marrow and peripheral blood smears revealed the presence of atypical lymphoid cells (Figure 3A and B). Bone marrow biopsy showed a bland infiltration by T lymphoproliferative disease in an intrasinusoidal pattern, supporting the diagnosis (Figure 3C and D). Flow cytometric (FC) analysis of the bone marrow aspirate revealed a population of abnormal cells (23.95%) with higher side scatter expressing CD2, CD3, CD56, and TCR-γδ as compared to normal T-lymphocytes (Figure 4). These cells were negative for CD4, CD8, CD57, CD19, CD10, CD33, CD25, and TDT. The bone marrow cytogenetic study revealed 46, XY, while molecular testing for bone marrow revealed that the clonal immunoglobulin heavy chain was negative, but TCR-γδ was positive.

FINAL DIAGNOSIS
These findings confirmed the diagnosis of HSTCL (γδ) stage IVB, which involved the spleen and bone marrow.

TREATMENT
The process of the therapy is shown in Table 1. Two cycles of inductive chemotherapy and residual disease test by FC showed that the abnormal cells had decreased from before (8.1% vs 23.95%). After the third cycle of chemotherapy, the FC analysis of the bone marrow suggested that aberrant initial cells increased, indicating disease recurrence. The patient was insensitive to chemotherapy, which means that he would not benefit from autologous SCT (auto-SCT). The patient agreed to undergo allogeneic
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Table 1 Treatment regimens and response evaluations

| No. | Regimen               | Dose                                                                 | Abnormal cells, % | Response |
|-----|-----------------------|----------------------------------------------------------------------|-------------------|----------|
| 1   | Hyper-CVAD            | CTX 300 mg/m² Q12H days 1-3 (mesna rescue); VDS 4 mg day 4, 11; DNR 45 mg/m² day 1; DEX 40 mg days 1-4, days 11-14 | 8.1               | PR       |
| 2   | MA                    | MTX 1.0 g/m²2 day 1; Ara-C 2 g/m²2 days 2-3 Q12H; methylprednisolone 30 mg/m²2 days 1-3 |                 |          |
| 3   | Hyper-CVAD            | CTX 300 mg/m² Q12H days 1-3 (mesna rescue); VDS 4 mg days 4, 11; DNR 45 mg/m²2 day 1; DEX 40 mg days 1-4, days 11-14 | 21.42             | PD       |
| 4   | ICE + chidamide       | IFO 5 g/m²2 day 1, CBP (AUC = 5 mg/mL per min) day 1, VP-16 100 mg/m²2 days 3-5; Chidamide: 20mg biw days 1-21 | 9.94              | PR       |
| 5   | Chidamide             | 30 mg biw days 1-21                                                  | 5.6               | CR       |

Cycle length for each course is 21 d; Abnormal cells%: Percentage of atypical lymphocytes as normal lymphocytes analysis by flow cytometric. CR: Complete remission; PR: Partial remission; PD: Progressive disease; Hyper-CVAD: Fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; CTX: Cyclophosphamide; VDS: Vindesine; DNR: daunorubicin; DEX: Dexamethasone; MA: Methotrexate, cytarabine, methylprednisolone plus; MTX: Methotrexate; Ara-C: Cytarabine; ICE: Ifosfamide, carboplatin, etoposide; IFO: Ifosfamide; CBP: Carboplatin; VP-16: Etoposide; AUC: AUC is converted to a patient-specific carboplatin dose (in mg) according to renal function by using the Calvert formula.

Figure 1 Baseline and follow-up positron emission tomography-computed tomography, which show the size and metabolism of the liver and spleen. A: During the first hospital visit, the patient showed significant enlargement of the spleen and mildly abnormal fluorodeoxyglucose accumulation in the spleen and liver; B: After chidamide combination therapy, no increased metabolism was observed in the liver.

SCT (allo-SCT), but no appropriate donor was found. Hence, we chose the novel drug chidamide and administered 20 mg tablets twice a week plus the adjusted-dose regimen of ifosfamide, carboplatin, etoposide (ICE) for salvage therapy. After one cycle, the number of abnormal cells decreased from 21.42% to 9.94%. Additionally, a follow-up PET-CT was performed and showed normal liver size and normalized increased FDG uptake (Figure 1B).

To ensure a better quality of life, the patient refused to restart chemotherapy and chose to continue with chidamide treatment to prevent disease relapse. Interestingly, after administration of chidamide 30 mg twice a week and monotherapy for 2 mo (3 cycles), the FC analysis showed 0.5% abnormal cells, which indicated complete remission (CR). Apart from the only side effect of grade 2 thrombocytopenia observed, chidamide single drug maintenance was well tolerated.

OUTCOME AND FOLLOW-UP

After 9 mo of chidamide therapy, follow-up bone marrow smear showed substantially increased pathological cells (32%), which indicated lymphoma progression. Though recommend with the rescue chemotherapy and allo-SCT or other targeted drugs (e.g.,
Figure 2  Morphology and immunohistochemistry analysis of spleen. A: Spleen shows atypical lymphocytes within the sinusoids; B-F: These cells tested positive for CD3, CD56, CD4, and TIA-1 but negative for Epstein-Barr virus-encoded RNA on in situ hybridization (20 × objective); G: Gene studies demonstrate T-cell receptor-γδ clonal re-arrangements. EBER: Epstein-Barr virus-encoded RNA.

Figure 3  Morphology and immunohistochemistry analysis of bone marrow and peripheral blood. A and B: Bone marrow aspirate smear (panel A) and blood smear (panel B) show atypical lymphocytes with round or irregular shape, less cytoplasm, irregular nuclear contours, and visible nucleoli (Wright-Giemsa, 1000 ×, oil); C and D: Bone marrow biopsy showed many atypical lymphocyte-infiltrated sinuses (panel C, hematoxylin and eosin staining, 400 ×) were positive for CD3 (panel C, 400 ×).

alemtuzumab), the patient and his family refused to chemotherapy. Unfortunately, the patient died 1 mo after lymphoma progression because of severe pneumonia and respiratory failure which was cause by leukopenia. Early during this admission, no other abnormalities were found which may imply other occult diseases involved. For this patient, a chidamide combined chemotherapy and single drug maintenance regimen achieved CR, OS of 15 mo, and duration of response of 9 mo.
**Figure 4 Flow cytometry analysis of the bone marrow.** A-C: The entire population of lymphoid cells is gated (panel A). These atypical lymphocytes, which are red in color, formed 23.95% of all the lymphocytes and are CD3 and CD56 positive (panel B), and they are composed almost entirely of CD2+ cells (panel C); D, E: The gated CD3+ atypical cells were CD5dim positive and CD7 negative (panel D), and CD4 and CD8 negative (panel E); F: These atypical CD3+ lymphocytes also expressed T-cell receptor-γδ.

**DISCUSSION**

To the best of our knowledge, this is the first report regarding the management of HSTCL with chidamide, a rare disease that showed recurrence with traditional chemotherapy and DOR of 9 mo.

As a rare disease, there has been no consensus about its treatment. Potent induction chemotherapy and allo-SCT may be the most common treatment strategies for HSTCL\[7\]. The first-line chemotherapy regimen of chemo-with-anthracycline regimen (CHOP, CVP, or Hyper CVAD/MA) is the top priority in majority of the patients to start with as the induction option. However, poor prognosis with much lower CR response rate (20%-40%)\[11\] as compared to that of nodal T-cell lymphomas and short time of relapse (8-16 mo) has long been the major concern.

The use of auto-SCT or allo-SCT in HSTCLs has been explored but not well defined in large clinical trials of HSTCL. A recent report from the American Society for Blood and Marrow Transplantation representing consensus opinion has recommended that transplant can be considered in this rare subtype in the case of first remission and relapse-sensitive patients\[7\]. Due to the limited or questionable benefit shown by auto-SCT in HSTCL, allo-SCT is more promising and well accepted as a front-line consolidation therapy in HSTCL as compared to the commonly adopted auto-SCT for most PTCLs (except ALK-positive anaplastic large cell lymphoma)\[12\]. A retrospective study performed by the European Bone Marrow Transplant Lymphoma Working Party that included 25 patients with HSTCL and treated with allo-SCT also showed a prominent prolonged median survival of 36 mo\[13\].

However, due to the low remission rate, only a small proportion of patients underwent SCT after initial remission. The T-Cell Project, which initiated the first prospective worldwide study of patients with aggressive T-cell lymphomas, showed that only 33% of 24 HSTCL patients underwent transplant (auto-SCT, 1; allo-SCT, 4) as consolidation therapy. Additionally, three patients underwent SCT in the salvage setting. Therefore, these patients with HSTCL still had a shortened median OS (13 mo) and a shortened median progression-free survival (11 mo)\[11\].

Therefore, there is an urgent need to incorporate novel agents in the therapy for
HSTCL. New targeted therapies such as pralatrexate, duvelisib, and romidepsin are emerging as potential treatments for PTCL[8]. However, due to its rarity, no large registry study would consider HSTCL as the inclusion criterion. Therefore, no attempt of a combination and maintenance treatment with HDAC inhibitor or other novel drugs for this rare subtype has been tested so far.

The regimen used in our case is described here. First, chidamide is an HDAC inhibitor that mediates chromatin remodeling by interfering with the binding between histone and DNA that increases the level of acetylation, suppresses T lymphoma cell growth, and promotes apoptosis[9]. SETD2 methyltransferase mutations occur in HSTCL and hypermethylation of CpGs around transcription start sites was associated with a lack of protein expression in HSTCL, which showed that the epigenetic drug chidamide would show effective results in HSTCL[10]. Second, chidamide and therapeutic chemotherapy have a synergistic effect of inducing apoptosis with DNA damage accumulation and repair defects. The mechanism is similar to the synergistic effect of low-dose decitabine added to the treatment of acute lymphocyte leukemia[11]. In PTCL, the HDAC inhibitor in combination with the ICE regimen has been shown to have a satisfying effect on relapsed/refractory PTCL, with a 75% (5/7) objective response rate and 100% CR (5/5). The median continuous response time can last for 7.2 mo[12]. To reduce the toxic side effects of co-medication, we reduced the dose of ICE regimen to 2/3 as well as chidamide to 20 mg twice a week, which was well tolerated. Third, HSTCL has already been shown to have a close relationship with immune dysfunction. It was reported that 10% of HSTCL cases occurred in patients with inflammatory bowel disease, who received tumor necrosis factor-alpha inhibitors and/or thiopurines[13]. Chidamide enhances the natural killer cells and antigen-specific cytotoxic T-cell-mediated tumor killer effect by inducing the expression of MHC class I-related proteins and NKG2D ligand on tumor cells[14]. Furthermore, chidamide is an orally administered convenient maintenance therapy that can improve the quality of life of the patients.

CONCLUSION

This case report is the first to demonstrate the effectiveness of chidamide combined with chemotherapy and single-drug maintenance therapy in a patient with HSTCL, who did not show improvement with traditional treatment. This report can be informative for the treatment of rare and poorly studied diseases.

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