



Relapsed Anaplastic ALK-Large Cell Lymphoma after Autologous Hematopoietic Stem Cell Transplantation Experiences Compound Realgar Natural Indigo Tablets: A Case Report

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Abstract

Anaplastic Large Cell Lymphoma (ALCL) is a rare type of malignant lymphoid disease with poor prognosis, especially ALK-ALCL. We evaluated the effectiveness and safety of Compound Realgar Natural Indigo Tablets (CRNIT) for a relapsed patient with ALK-ALCL after autologous Hematopoietic Stem Cell Transplantation (auto-HSCT). The patient was diagnosed with pathology of right inguinal lymph node enlargement. Partial Remission (PR) was achieved after two cycles of CHOP chemotherapy, and the patient had Stable Disease (SD) after sequential four cycles of CHOP chemotherapy, followed by achieved to Complete Remission (CR) one after local radiotherapy. Two months later, the patient experienced her first relapse and only achieved PR after four cycles of GDP chemotherapy. CR2 was achieved by auto-HSCT. The patient underwent the second relapse of disease at five months after auto-HSCT, manifesting as enlarged left inguinal and abdominal lymph nodes. Chidamide displayed transient curative effect accompanied by the grade of III myelosuppression. Large sheet-like red papule were gradually present throughout double lower limbs and the left lateral thigh. The CRNIT at 1.35 g was given orally three times daily. Efficacy was obvious and without severe adverse reactions especially in term of papule, lasting thirteen months. Finally, the patient died of pulmonary infection due to myelosuppression after chemotherapy. Even so, the CRNIT is a feasible therapy for relapsed patient with ALK-ALCL to buy time for more effective means and avoid side effects of chemotherapy.

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Introduction

Peripheral T-Cell Lymphoma (PTCL) is a rare type of malignant lymphoid disease that originates from mature post-thymic T-lymphocytes. It displays significant heterogeneity in biological behavior and clinical manifestation. Anaplastic Large Cell Lymphoma (ALCL), one kind of PTCL, is highly malignant with few treatment options, in especial ALK negative ALCL (ALK-ALCL). About 50% of patients experience relapses even after treatment with autologous Hematopoietic Stem Cell Transplantation (auto-HSCT), and the 5-year Overall Survival (OS) is less than 30% [1]. The lack of effective treatment options exacerbates the outcome of patients suffered from relapse after auto-HSCT. In this study, one patient with ALK-ALCL who relapsed after autologous hematopoietic stem cell transplantation achieved good effect after Compound Realgar Natural Indigo Tablets (CRNIT).

Case Presentation

Materials and methods

The patient, a 54 years old female found small red lump in the right hip (maximum size of 30 mm × 25 mm) and right inguinal lymphadenectasis (maximum size of 28.8 mm × 14.2 mm) on May 2015. The enlarged lymph nodes were flexible, good activity and no tenderness. No efficacy was achieved after anti-infective treatment of penicillin, cefuroxime and levofloxacin for intermittent one month. Pathology of lump in right hip showed squamous epithelium with lymphocytic infiltration. Biopsy and immunohistochemical staining of the right inguinal lymph nodes were as follows: CD43+, Mum-1+, Bcl-6-/+, CD30(+), Ki-67 (about 60%+), CD10-, CD23-, CD20B+, Pax-5B+, CD1a B+, CD2+, CD3 T+, CD5 T+, CD68 [tissue cell+], S100 [tissue cell+], CD117-, CD21-, CD138 [plasma cell+], CD35-, CD34-, CD79a-, CD38 [plasma-cell+], MPO [scattered+],

CK-, ALK-, CD7-, EMA and EBER negative. After a comprehensive systemic examination, the patient was diagnosed with IIA stage of ALK-ALCL, IPI score of 0 point. Between December 8th 2015 and April 25th 2016, the patient achieved Partial Remission (PR) after two cycles of CHOP chemotherapy and Stable Disease (SD) after four cycles of sequential CHOP chemotherapy. Between June 21st and July 28th 2016, conformal intensity-modulated radiotherapy of DT 50Gy/25F was performed on the right groin and hip. The efficacy evaluation achieved Complete Remission (CR) 1 on October 2016. However, the patient underwent the first relapse with multiple enlarged lymph nodes two months later, a maximum size of 30 mm × 16 mm. The enlarged lymph nodes were hard with tenderness and difficult to differentiate from the surrounding boundaries. PR was obtained after 4 cycles of GDP chemotherapy during three months, followed by autologous peripheral blood hematopoietic stem cells mobilized by Granulocyte Colony-Stimulating Factor (G-CSF) were collected after chemotherapy of GDP+VP-16. On May 13th 2017, auto-HSCT was performed following pretreatment with whole body radiotherapy (TBI) + Busulfan (Bu). Hematopoietic function was successfully reconstructed and CR2 was achieved at three months after auto-HSCT. However, the second relapse occurred two months later with pathology of enlarged lymph nodes on the left groin and abdominal wall. Chidamide at dose of 30 mg (twice a week) combined with Prednisone (PDN) were given orally on October 23rd 2017. The patient achieved PR with the grade of III myelosuppression and reduced the dose of Chidamide to 20 mg on her own. As a result, the disease progressed rapidly with large sheet-like red papules throughout double lower limbs and the left lateral thigh. Several of the papules were fused, and the left groin was swollen. The effect was no satisfaction even though the dose of Chidamide was increased to 30 mg. So, the patient was orally with CRNIT at 1.35 g, three times daily.

Result and Discussion

Papules in the left lateral thigh darkened to a pink and shrank after treatment of two months (Figure 1). PR was achieved without severe adverse reactions, lasting thirteen months. The patient died of pulmonary infection due to myelosuppression after chemotherapy finally.

Arsenic trioxide (As_2O_3) has been successfully used for the treatment of Acute Promyelocytic Leukemia (APL) as a traditional Chinese medicine. The mechanism of action of As_2O_3 involves promoting cell apoptosis, partial differentiation, regulating apoptosis-related gene and biological pathways, prolonging the doubling time and suppressing cell cycle progression. In recent years, As_2O_3 has been increasingly used in clinical and experimental studies for several other hematological diseases such as lymphoma. *In vitro* studies had demonstrated that As_2O_3 could inhibit the proliferation of malignant lymphoma cell lines [2] by inducing apoptosis through pathways such as CD95/CD95L. It was demonstrated that As_2O_3 had the efficacy of anti-angiogenic effect by down-regulating Vascular Endothelial Growth Factor (VEGF). As_2O_3 combined with Doxorubicin (ADM) had been shown to promote up-regulation of apoptotic proteins BAX, p53 and Caspase-3 in B cell lymphoma cell lines (Raji), and to down-regulate anti-apoptotic proteins BCL-2, NF- κ B and Survivin. In addition, As_2O_3 could not only increase the expression of autophagy-related proteins Beclin-1 and LC3-II, but also decrease the expression of p62/SQSTM1 [3]. A previous study also confirmed that As_2O_3 delayed the growth and induced apoptosis of human follicular

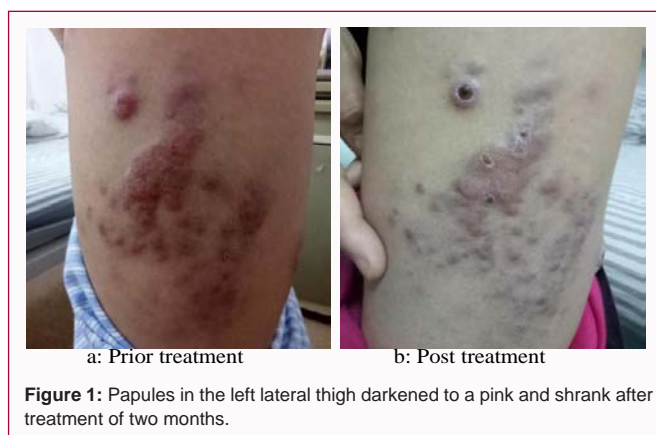


Figure 1: Papules in the left lateral thigh darkened to a pink and shrank after treatment of two months.

lymphoma cells (MCL) by inhibiting the expression of cyclin D1 and up-regulating apoptosis-related genes [4].

CRNIT is a compound preparation of drugs consists of realgar, indigo naturalis, *Pseudostellaria heterophylla* and the root of red-rooted salvia. Realgar is the monarch drug of CRNIT, with the main components of Tetra-Arsenic Tetrasulfide (As_4S_4) and As_2O_3 , inhibiting cell proliferation and inducing cell differentiation and apoptosis. Naturalis indigo as the ministerial drug of CRNIT has significant synergistic effects in combination with realgar. The root of red-rooted salvia activates blood circulation and removes blood stasis, while *Pseudostellaria heterophylla* possess the ability of replenishing to invigorate the spleen. They are considered the adjuvant components of CRNIT. CRNITA is an oral preparation, which is less toxic, safer and easier to administer compared to As_2O_3 . However, As_4S_4 plays a pivotal role in the treatment of CRNIT which is beneficial to APL. Furthermore, indirubin, the antitumor active ingredient of naturalis indigo, enhances the ability of apoptosis induced by As_4S_4 through the mitochondrial apoptotic pathway, accompanied by the disruption of BAX genetic [5]. A study displayed that realgar induced the apoptosis and differentiation of ATRA-sensitive cell line NB4 and ATRA-resistant cell line MR2 [6]. The mechanism of apoptosis in NB4, HL-60 and K562 cells induced by realgar is associated with inhibiting the expression of BCL-2 and PNAS-2, telomerase activity and the MAPK pathway [7-8].

CRNIT has also been used in other malignant hematological diseases such as lymphoma. Realgar induces apoptosis of human T-cell lymphoma cell line (Jurkat, CEM-T) and inhibits cell proliferation depending on arresting cells in G2/M phase, down-regulating Bcl-2 and adding AP02.7 protein expression [3] and B cell lymphoma cell lines (Raji cells) [4]. Nano-realgar was regarded to induce apoptosis and autophagy in K562 leukemia cell lines [9]. Realgar is a potential multidrug-resistant inhibitor owing to its ability to down-regulate mRNA levels of multidrug-resistant ABC family genes, which decreasing the IC50 of ADM in drug-resistant MCF-7/ADM cancer cell lines and reversing the drug resistance of MCF-7/ADM cells to ADM. Indirubin and derivatives also competitively combined with ATP binding site of Cyclin-Dependent Kinase (CDK) and Glycogen Synthase Kinase 3B (GSK-3B) in addition to significant inhibitory effects on CDK1, CDK2 and CDK4. Moreover, both anti-angiogenic properties and regulates the expression of apoptosis-related genes were observed [10]. Indirubin had the equal ability of inhibiting growth and inducing apoptosis in malignant lymphocytes such as Jurkat cells and B-cell lymphoma cell lines (IM9, Reh6) [5] with little toxicity to the liver, kidney and bone marrow.

In this case report, a patient presented with subcutaneous nodules was diagnosed with ALK-ALCL by lymph node biopsy. CR1 was achieved after chemotherapy and radiotherapy. However, relapse occurred two months later. Auto-HSCT plays a main role in relapsed ALK-ALCL. PR and CR2 was achieved through second-line chemotherapy regimen and auto-HSCT respectively. However, the patient suffered from the second relapse at five months after Auto-HSCT. Given that there was a shortage of bone marrow reserve function after auto-HSCT, the patient was administered a combination of Chidamide and PDN because of shortage of bone marrow reserve function after auto-HSCT and effectiveness of Chidamide. But the patient experienced the grade of III myelosuppression. The disease progressed rapidly after reduced Chidamide dose. CRNIT was chose rather than routine chemotherapy in the face of poor bone marrow reserve function. It was inspiring that PR lasted for thirteen months without significant myelosuppression and other serious side effects. At present, there are little reports of CRNIT for ALCL. Therefore, CRNIT probably is a new treatment option for refractory and recurrent ALK-ALCL. However, there are some limitations in the study. It would be necessary to perform a prospective study with large samples aiming to demonstrate efficacy and safety of CRNIT. The exact mechanism of CRNIT remains to be explored.

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