Successful Treatment, with Chemotherapy and Intravenous Administration of Ascorbic Acid, of a Patient with Peripheral T-Cell Lymphoma, Not Otherwise Specified

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Abstract: Here, we report the case of a 64-year-old man with peripheral T-cell lymphoma, not otherwise specified, who complained of diffuse lymphadenopathy and pancytopenia. This patient received the CHOP regimen followed by the CHP plus brentuximab vedotin regimen, and eventually experienced severe adverse effects, such as leukocytopenia and thrombocytopenia. He was then intravenously administered high doses of ascorbic acid to enhance the effects of chemotherapy drugs and reduce the intensity of the side effects. Positron emission tomography-computed tomography revealed a complete response of the lesions to combination therapy. This case report demonstrated the feasibility, efficacy, and acceptable toxicity of high-dose ascorbic acid in patients undergoing chemotherapy.

Keywords: Ascorbic acid, Peripheral T-cell lymphoma, Chemotherapy, Quality of life, EORTC QLQ-C30, Instrumental activities of daily living.

INTRODUCTION

Peripheral T-cell non-Hodgkin lymphoma (PTCL), not otherwise specified (NOS), is the most common PTCL subtype, accounting for at least 25% of all PTCL cases [1, 2]. It mostly affects adult patients, predominantly males, with a median age at presentation of 60 years [2, 3]. The prognosis of most PTCL subtypes is poor, with a 5-year survival rate of 30–40%. Currently, there is no clear consensus regarding the optimal management of patients with newly diagnosed PTCL. While cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP-like regimens are preferred as first-line treatments for PTCL-NOS [3, 4], it has recently been demonstrated that frontline treatment of patients with PTCL with brentuximab vedotin (A) plus CHP (cyclophosphamide, doxorubicin, and prednisone) (A + CHP) provides clinically meaningful improvements in progression-free survival and overall survival [5]. However, upfront autologous stem cell transplantation may not provide survival benefits for patients with PTCL-NOS [6]. Few effective options are available for salvage pathways. A high rate of disease relapse or progression has been shown, yielding a 5-year survival rate of 32–45% [4]. Therefore, a new strategy for the treatment and management of patients with PTCL-NOS is required. Over the past century, the notion that ascorbic acid (AA/ vitamin C) can be useful for cancer treatment has generated much controversy [7, 8]. Nevertheless, there is new knowledge on the pharmacokinetic properties of vitamin C and intravenous administration of high doses of AA has been shown to be a potential alternative to cancer therapy [8]. Preclinical studies have provided evidence for the anticancer effects of vitamin C and demonstrated its synergy with chemotherapeutic agents. The early phase human trial was too small to statistically confirm its efficacy but demonstrated a significant reduction in chemotherapy-induced adverse effects in patients receiving vitamin C. It has also been suggested that treatment with high-dose parenteral AA improves the quality of life of patients with cancer, and in combination therapy, vitamin C protects normal tissues from the toxicity caused by chemotherapeutic agents [9].

Herein, we report the case of a man with PTCL-NOS who was successfully treated with chemotherapy in combination with high-dose AA. Treatment efficacy was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, whereas

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adverse events were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0. The serum concentrations of AA were measured immediately after administration, because the concentration of AA in plasma has been shown to peak immediately after intravenous administration of high doses of AA and to decrease to approximately one fifth of this level within 4 h, due to rapid clearance [10]. Patient-reported outcomes were used to evaluate the quality of life (QOL) during chemotherapy. We used the EORTC QLQ-C30 to assess the global health status, physical and mental functioning, and symptoms–such as fatigue, appetite loss, and constipation–of the patient [11, 12]. We also used the Tokyo Metropolitan Institute of Gerontology index of competence (TMIG-IC) to assess the patient's instrumental activities of daily living (IADL) [13] and the Geriatric Depression Scale 15-item version (GDS15) to assess for depressive symptoms [14, 15]. This study was performed according to the guidelines of the Declaration of Helsinki and those from the Nagoya Memorial Hospital; the patient gave written informed consent to participate in the study.

CASE PRESENTATION

A man aged 64 with diffuse lymphadenopathy and pancytopenia presented for a medical check-up at Nagoya Memorial Hospital. Bone marrow involvement was subsequently detected using bone marrow aspiration and positron emission tomography-computed tomography (PET-CT). The pathological diagnosis of the biopsy specimens obtained from the inguinal lymph nodes of the patient was PTCL-NOS. CHOP therapy was initiated and, after three cycles, peripheral neuropathy due to vincristine was observed. Therefore, brentuximab vedotin was used instead of vincristine and another three cycles of A + CHP therapy were administered. The activity of red cell glucose-6-phosphate dehydrogenase (G6PD) was determined at the IVC Analysis Center (Fujioka, Japan), because patients with G6PD deficiency showed hemolytic anemia following high-dose intravenous ascorbate therapy [16]. After confirming that the value of G6PD (8.5 U/gHb) was within normal limits, a small starting dose of 12.5 g of AA was administered, followed by a second dose of 25 g AA in 5 days later. Subsequently, 50 g of AA was administered once or twice a week (diluted from a stock solution of preservative-free AA at 500 mg/mL; Mylan Pharmaceuticals ULC, Etobicoke, ON, Canada) according to the Riordan IVC protocol [17]. At each administration, Vitamin C, dissolved in 500 mL of distilled water, was administered intravenously at a rate of 0.5 g/min. Immediately after administration, the serum concentration of vitamin C was within a 450–550 mg/dL range. The patient's clinical course is shown in Figure **1**, including the schedule of chemotherapy and intravenous administration of high-dose AA as well as the laboratory data of complete blood cell counts. Notably, the six cycles of chemotherapy induced complete disappearance of the lesions (Figure **2**). Table **1** shows the chronological changes in the

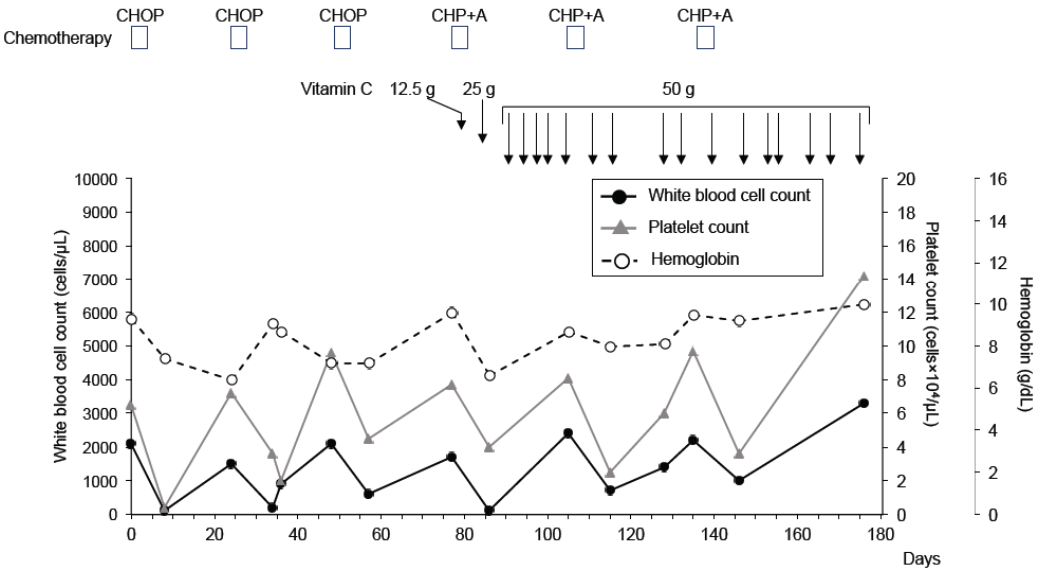

Figure 1: Clinical course of a case of a 64-year-old man with peripheral T-cell lymphoma, not otherwise specified, who was first treated with a CHOP regimen and then with a CHP-based regimen in combination with high-dose ascorbic acid.

CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CHP + A, cyclophosphamide, doxorubicin, and prednisone plus brentuximab vedotin

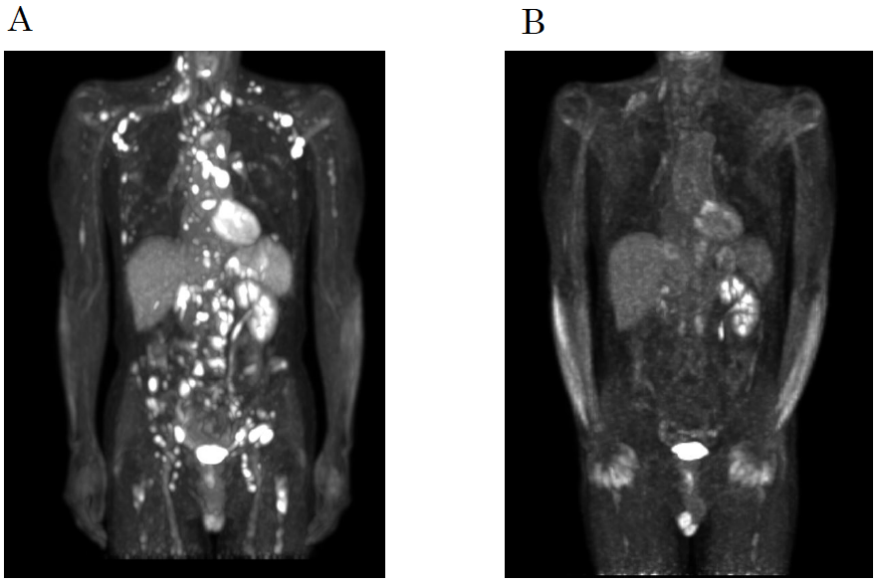

Figure 2: Positron emission tomography-computed tomography scan showing (**A**) multiple enlarged lymph nodes and bone marrow infiltration before chemotherapy. (**B**) These lesions disappeared after chemotherapy, consisting of three cycles of CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone) and three cycles of CHP (cyclophosphamide, doxorubicin, and prednisone) plus brentuximab vedotin, which was evaluated as complete response to the combination therapy of chemotherapy and high-dose vitamin C.

Table 1: Chronological changes in the EORTC QLQ-C30, Tokyo Metropolitan Institute of Gerontology Index of Competence, and geriatric depression scale scores of a 64-year-old man with peripheral T-cell lymphoma, not otherwise specified, along with his blood transfusion and administration of granulocyte-colony stimulating factor history

	Before	Day8	Day24	Day35	Day75	Day85	Day114	Day145	Day180
EORTIC QLQ-C30									
GH	33.3	0	33.3	0	16.7	0	33.3	58.3	66.7
Functional scales									
Physical scales	60	13.3	80	26.7	60	26.7	46.7	60	86.7
Emotional scales	16.7	16.7	75	8.3	75	50	83.3	100	100
Symptom scales									
Fatigue	77.7	100	33.3	100	88.9	100	33.3	44.4	33.3
Appetite loss	33.3	100	33.3	66.7	66.7	66.7	33.3	66.7	0
Constipation	0	66.7	0	100	66.7	66.7	66.7	66.7	33.3
TMIG-IC	13	4	8	4	13	6	13	13	13
GDS15	7	12	8	10	10	8	7	6	4
Blood transfusion									
Packed red blood cells	#1		#2, 3	#4, 5		#6,7,8	#9		
Platelets		#1,2,3	#4,5		#6	#7,8			
Granulocyte-colony stimulating factor									
Pegfilgrastim		⬆				⬆			
Filgrastim			29-36 ⟷		55-62 ⟷		110-7 ⟷	138-47 ⟷	

GH: global health status.
TMIG-IC: Tokyo Metropolitan Institute of Gerontology Index of Competence.
GDS15: Geriatric Depression Scale 15-item version.

patient's EORTC QLQ-C30, TMIG-IC, and GDS15 scores, along with his history of blood transfusion and administration of granulocyte-colony stimulating factor. After starting intravenous administration of high-dose AA (Day 79), blood transfusion frequency was decreased, while QOL scores were gradually improved: EORTIC QLQ-C30 (at days 85, 114, 145, and 180), global health status (0, 33.3, 58.3, and 66.7, respectively), physical scales (26.7, 46.7, 60, and 86.7, respectively), and emotional scales (50, 83.3, 100, and 100, respectively). At the same time, all symptom scales to assess fatigue, appetite loss, and constipation decreased, which enhanced IADL and alleviated depressive symptoms.

DISCUSSION

A recent review described the evidence supporting the therapeutic potential of vitamin C: first, the biological functions and chemical properties of vitamin C; second, the mechanisms by which high-dose vitamin C can selectively kill cancer cells; and third, perspectives on the future of vitamin C research as a cancer treatment [8]. A preclinical study showed that pharmacological concentrations of vitamin C are pro-oxidants, generating hydrogen peroxide-dependent cytotoxicity against a variety of cancer cells [18]. For most of the cancer cell lines examined, the concentration of vitamin C required to cause a 50% decrease in cell survival (EC50) was approximately 10-15 mM (175-264 mg/dL). The EC50 of the lymphoma cell line JLP119 was very low (2 mM = 35 mg/dL), suggesting that lymphoma may be one of the most sensitive tumors to intravenous treatment with vitamin C. In addition, a phase I clinical trial of high-dose AA, conducted in patients with non-Hodgkin's lymphoma, indicated that high-dose parenteral vitamin C should be tolerable and suitable for clinical use [19].

CONCLUSION

This case report suggests that combination therapy of CHP-based regimens and 50g of parenteral vitamin C should be safe for patients with PTCL-NOS. Moreover, off-label administration of high-dose AA might be useful for improving QOL by reducing adverse effects in patients receiving chemotherapy.

AUTHORS' CONTRIBUTIONS

KI, AT, and SK contributed to study conception and design. CT, HK, TY, and SK treated the patient with PTCL-NOS. CT, KI, and YT contributed to manuscript writing. KI and SK interpreted radiological findings. All the authors have read and approved the final version of the manuscript.

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DECLARATION OF CONFLICTING INTERESTS

The authors declare that there are no relevant financial or non-financial competing interests to report.

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