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ORIGINAL ARTICLE

Alemtuzumab plus CHOP as front-line chemotherapy for patients with peripheral T-cell lymphomas: a phase II study

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Abstract
Purpose The present study was conducted to evaluate the safety and efficacy of alemtuzumab plus CHOP chemotherapy for patients with peripheral T-cell lymphomas (PTCLs).
Patients and methods Twenty patients with newly diagnosed PTCLs were enrolled. The treatment consisted of classical CHOP plus alemtuzumab (10 mg i.v. on day 1 and 20 mg i.v. on day 2 in the first cycle, then 30 mg i.v. on day 1 in the subsequent cycles) based on 3-week intervals.
Results Thirteen complete responses (65.0%) and three partial responses (15.0%) were confirmed, giving an overall response rate of 80.0%. The estimated event-free survival at 1 year was 43.3%. The most severe hematologic adverse event was neutropenia, which occurred with a grade-4 intensity in 18 patients (90.0%). Also, febrile neutropenia was observed in 11 patients (55.0%). Five patients (25%) experienced cytomegalovirus (CMV) reactivation, while three patients developed CMV diseases, such as pneumonitis or retinitis. There were two treatment-related deaths. Based on the high incidence of the adverse infectious and hematologic events, the current study was closed after 20 of the planned 43 patients had been enrolled.
Conclusion The alemtuzumab plus CHOP chemotherapy seemed to produce active antitumor activity in terms of the complete response rates in patients with PTCLs. However, since high infectious and hematologic toxicities were observed, careful monitoring and early treatment are needed to prevent treatment-related mortality.

Keywords Peripheral T-cell lymphoma · CHOP · Alemtuzumab

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Introduction

Patients with aggressive non-Hodgkin's lymphomas (NHLs) can be cured using various chemotherapy regimens, yet the cure rates vary according to the pretreatment prognostic variables. Despite several attempts at devising more effective regimens, CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) combination chemotherapy, with a 44% complete response rate, 42% 3-year disease-free survival rate, and 54% 3-year overall survival rate, is still considered as the best available chemotherapeutic regimen for aggressive NHLs [1–3].

Meanwhile, peripheral T-cell lymphomas (PTCLs), originally described in the REAL classification [4], are

uncommon subsets of lymphomas that generally have a poor prognosis [5]. In contrast to B-cell NHLs, where major therapeutic advances have recently been made with rituximab [6, 7], a monoclonal anti-CD20 antibody, the treatment of PTCLs remains a challenge.

Alemtuzumab is a humanized immunoglobulin G1 anti-CD52 monoclonal antibody that binds to the cell membrane of more than 95% of all normal human blood lymphocytes, as well as to most B- and T-cell lymphomas [8]. Malignant T cells also appear to express extraordinary high numbers of CD52 cell surface molecules (approximately 500,000 molecules per lymphocyte) [9]. Thus, several clinical studies have demonstrated that alemtuzumab is effective for the treatment of B-cell chronic lymphocytic leukemia, T-cell prolymphocytic leukemia (T-PLL), and mycosis fungoides/Sezary syndrome (MF/SS) [10–12]. Enblad et al. also recently reported that alemtuzumab as a single agent exhibited promising antitumor activity in patients with relapsed or chemotherapy-refractory PTCLs, although it was associated with significant hematologic toxicity and infectious complications [13]. However, there is no published data on the effectiveness of alemtuzumab as a frontline treatment for PTCLs.

Accordingly, the present pilot study was conducted to evaluate the safety and efficacy of alemtuzumab plus CHOP as a frontline chemotherapy for patients with PTCLs.

Patients and methods

Eligibility criteria

The patients included in this study were required to meet with the following eligibility criteria: (1) newly diagnosed PTCLs, except cutaneous T-cell lymphomas and anaplastic lymphoma kinase-positive anaplastic large-cell lymphomas; (2) age between 17 and 65 years; (3) Eastern Cooperative Oncology Group Scale performance status of 2 or less; (4) at least one measurable lesion; (5) adequate function of bone marrow (WBC count $\geq$ 4,000/μl and platelet count $\geq$ 75,000/μl), liver (serum bilirubin level $\leq$ 2.0 mg/dl and serum transaminase level $\leq$ three times the upper limit of the normal range), and kidney (serum creatinine level $\leq$ 1.5 mg/dl); (6) normal cardiac function; (7) no other severe medical conditions; and (8) no other active malignancy. The institutional review board of each author's institution approved the protocol, and written informed consent was obtained from all patients before enrollment.

Disease evaluation

All cases were reviewed by an expert hematopathologist for diagnostic confirmation and categorized according to the WHO classification. PTCLs were diagnosed by the expression of one or more pan-T-cell antigens (CD45RO, CD2, CD3, and CD7) and T-cell-associated antigens (CD4 or CD8), as well as by the absence of pan-B-cell antigens (CD19 and CD20). Rearrangements of T-cell receptor-γ were used to confirm the monoclonality of PTCL. In addition, the expression of CD30 antigen for anaplastic large cell lymphoma and CD56 antigen for extranodal NK/T-cell lymphoma was also examined. The immunohistochemistry for CD52 antigen on the lymphoma cells was not analyzed because it was expressed on most B and T lymphoma cells in the previous study [8]. The pretreatment evaluation comprised complete blood cell counts, routine chemistry measurements, including serum lactate dehydrogenase (LDH), a chest and abdominal CT scan, bone marrow examination, and other tests when clinically indicated. The disease stage was determined using the Ann Arbor criteria, and all patients were evaluated for the presence of risk factors according to the International Prognostic Index (IPI) based on age, stage, performance status, number of extranodal disease sites, and LDH.

Study treatment

The treatment consisted of classical CHOP (cyclophosphamide 750 mg/m^2 i.v., doxorubicin 50 mg/m^2 i.v., vincristine 2 mg i.v. on day 1, and prednisone 100 mg p.o. on day 1–5) plus alemtuzumab (10 mg i.v. on day 1 and 20 mg i.v. on day 2 in the first cycle, then 30 mg i.v. on day 1 in the subsequent cycles) based on 3-week intervals. Since alemtuzumab monotherapy with a dose of 30 mg intravenously three times a week caused severe infectious complications in the previous study [13], alemtuzumab of 30 mg per 3 weeks was added to cytotoxic CHOP chemotherapy in the present study. All patients were premedicated with a acetaminophen 1,300 mg orally and an intravenous injection of diphenhydramine 50 mg and hydrocortisone 100 mg 30 min before the alemtuzumab to prevent any hypersensitivity reactions. Trimethoprim/sulfamethoxazole, twice daily, three times a week, and acyclovir 600 mg, twice daily, were administered starting on day 8 and continued during the study and up to a minimum of 2 months following discontinuation of the alemtuzumab therapy. The prophylactic use of a colony-stimulating factor (CSF) was not permitted in the first cycle. However, if grade IV neutropenia or febrile neutropenia developed, prophylactic CSF could be given in the subsequent cycles. The plan for patients with a low or low-intermediate risk IPI was six courses of chemotherapy, followed by radiotherapy at bulky sites. Meanwhile, autologous stem cell transplantation (SCT) was permitted for patients with a high or high-intermediate risk IPI after completion of the chemotherapy. Chemotherapy was withheld for 1 week until the neutrophil count was higher than 1.5×10^3/μl and the platelet count

more than 75,000/μl. If febrile neutropenia or grade IV neutropenia lasting over 7 days occurred, the starting dose of cyclophosphamide and doxorubicin was reduced by 25% in the subsequent course of treatment.

Response and safety assessment

The patient response was evaluated after every two courses of treatment, 1 month after the completion of treatment, and thereafter every 3 months during follow-up according to the NHL response criteria [14]; also the toxicity was evaluated and graded according to the National Cancer Institute Common Toxicity Criteria (NCI CTC) version 3.0 grading system. Complete blood counts were performed weekly during the first cycle and every cycle thereafter, and biochemical tests were performed before each cycle.

Cytomegalovirus (CMV) antigenemia by direct staining of leucocytes from peripheral blood using an antibody pool directed against pp65 was also monitored before each cycle. CMV reactivation was defined as any positive level in a CMV pp65 antigenemia assay, and CMV disease was defined as a symptomatic CMV infection.

Statistical analysis

The primary endpoint of the present study was to evaluate the response rate of the study treatment. The current trial used a two-stage optimal design, as proposed by Simon, with an 80% power to accept the hypothesis and 5% significance to reject the hypothesis [15]. Also, the current trial was designed to detect a response rate of 70% as compared to a minimal, clinically meaningful response rate of 50%. Accordingly, the total sample size was 43 patients with a measurable disease. All valuable data are reported using the intent-to-treat patient population. Overall survival was measured from the study entry until the date of death or last follow-up, while event-free survival was calculated from the study entry until disease progression, relapse, or death from any cause. The overall survival curves were plotted using the Kaplan–Meier method, and the statistical data obtained using an SPSS software package (SPSS 11.0 Inc., Chicago, IL, USA).

Results

Patient characteristics

Twenty patients were enrolled between May 2005 and April 2006 from five medical centers in Korea, and the patient characteristics are summarized in Table 1. PTCLs, unspecified (50.0%), were the most common histological subtype. Nine patients (45.0%) had Ann Arbor stage III or IV disease at diagnosis, and eight (40.0%) patients were classified as high-intermediate or high risk according to the IPI scoring system. All patients were IgG-positive to CMV.

Table 1 Patient characteristics

Characteristic	Number of patients (%)
Age (years)	
Median	50.5
Range	20–65
Gender	
Male	14 (70.0)
Female	6 (30.0)
ECOG performance status	
0–1	16 (80.0)
2	4 (20.0)
Histologic subtype	
Peripheral T cells, unspecified	10 (50.0)
Extranodal NK/T cells, nasal type	3 (15.0)
Angioimmunoblastic T cells	3 (15.0)
ALK negative anaplastic large cells	2 (10.0)
Subcutaneous panniculitis-like T cells	2 (10.0)
Stage	
I–II	11 (55.0)
III–IV	9 (45.0)
International prognostic index	
Low	10 (50.0)
Low-intermediate	2 (10.0)
High-intermediate	5 (25.0)
High	3 (15.0)

ALK anaplastic lymphoma kinase

Response to treatment

All patients were assessable for response. Thirteen complete responses (65.0%) and three partial responses (15.0%) were confirmed, giving an overall response rate of 80.0% (95% CI; 58.3–96.3%), while one stable disease and three progressive disease were observed, respectively. Among the ten patients with PTCLs, unspecified, eight patients exhibited complete responses, while two exhibited partial responses. The responses according to the histologic subtype are also summarized in Table 2. Autologous SCT as a consolidation therapy was performed on four patients. Among the seven patients who relapsed or progressed during the study, five patients received salvage treatment (four DHAP chemotherapy and one ICE chemotherapy, followed by autologous SCT). Nine patients had died at the time of the present evaluation. The causes of death were as follows: disease progression ($n = 6$), pneumonia ($n = 2$), and sudden death during autologous SCT ($n = 1$). The median event-

Table 2 Response according to histologic subtype

Histologic subtype (number)	Response (%)			
	CR	PR	SD	PD
Peripheral T cell, unspecified (10)	8 (80.0)	2 (20.0)		
Extranodal NK/T cells, nasal type (3)	1 (33.3)		1 (33.3)	1 (33.3)
Angioimmunoblastic T cells (3)	2 (66.6)			1 (33.3)
ALK negative anaplastic large cells (2)	1 (50.0)	1 (50.0)		
Subcutaneous panniculitis-like T cells (2)	1 (50.0)			1 (50.0)

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *ALK* anaplastic lymphoma kinase

free and overall survival was 255 (95% confidential interval, 124–406) and 265 (95% confidential interval, 223–307) days, respectively, at a median follow-up duration of 219 (range, 35–368) days (Fig. 1). The estimated event-free and overall survival rate at 1 year was 43.3 and 44.3%, respectively (Fig. 1).

Toxicity

A total of 90 cycles (median 5.5, range one to six cycles) were administered to the 20 patients assessable for toxicity.

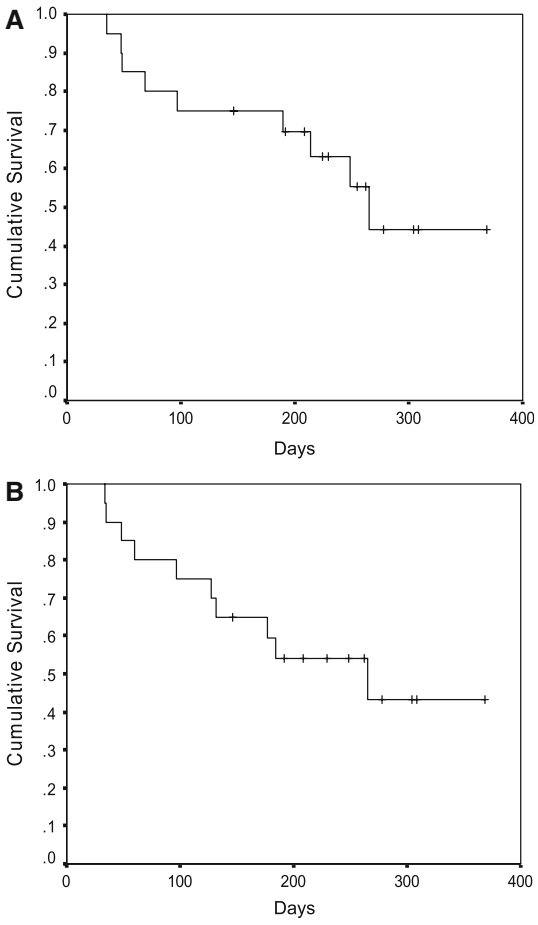

Fig. 1 Survival curves: **a** estimated 1-year overall survival rate and **b** event-free survival rate for all patients were 44.3 and 43.3%, respectively

Eleven patients (55.0%) completed the planned six cycles of treatment, while the remaining patients were withdrawn due to toxicity ($n = 4$) and/or progressive disease ($n = 5$). No severe infusion-related adverse events, such as hypotension, dyspnea, or bronchospasm, were observed.

The most severe hematologic adverse event was neutropenia, which occurred with a grade-4 intensity in 18 patients (90.0%) (Table 3). Also, febrile neutropenia was observed in 11 patients (55.0%), and treated with G-CSF and empirical antibiotics. Six (33.3%) patients received prophylactic G-CSF treatment after grade-4 neutropenia or febrile neutropenia, and only one patient developed same neutropenia in the subsequent cycles. The dose was reduced in 11 patients (55.0%) and treatment was delayed in eight patients (40.0%) due to hematologic toxicity. Nausea and vomiting were common non-hematological toxicities. Grade 1/2 nausea and vomiting were observed in 50.0 and 40.0% of the patients, respectively.

Cytomegalovirus reactivation occurred in five patients after a median of 12 weeks (range, 6–15 weeks). Two of the five patients presented with fever only, two patients had retinitis, and one patient had retinitis and pneumonitis. CMV reactivation or disease was treated with ganciclovir or foscarnet, yet one patient died of pneumonitis and one patient with retinitis had a sequela of visual disturbance after resolution of the CMV antigenemia. One patient in PR developed pseudomonas-induced pneumonia and a lung abscess after three cycles of the study treatment, which was related to cytopenia. Despite aggressive treatment of antibiotics and G-CSF, the patient died of septic shock and multi-organ failure. Also, one patient with high-risk IPI, who was in CR after six cycles of study treatment, died suddenly 7 days after autologous SCT for consolidation. Grade-4 neutropenia, fever, and mucositis were observed; however, there was no sign of pneumonia or bacteremia before death.

Discussion

Peripheral T-cell lymphomas are clinically aggressive and have a worse prognosis than high-grade B-cell lymphomas. As such, fewer than 40% of patients are expected to be

Table 3 Adverse reactions

	NCI-CTC grade: no. (%) of patients (n = 20)			
	Grade 1	Grade 2	Grade 3	Grade 4
Hematologic				
Anemia	5 (25.0)	7 (35.0)	5 (25.0)	1 (5.0)
Leukopenia		2 (10.0)		18 (90.0)
Neutropenia	1 (5.0)	1 (5.0)		18 (90.0)
Lymphopenia		1 (5.0)		19 (95.0)
Thrombocytopenia	6 (30.0)		6 (30.0)	
Non-hematologic				
Nausea	7 (35.0)	3 (15.0)		
Vomiting	4 (20.0)	4 (20.0)		
Stomatitis	2 (10.0)	2 (10.0)	1 (5.0)	
Diarrhea	1 (5.0)			
Constipation	4 (20.0)	1 (5.0)		
Neuropathy	3 (15.0)	3 (15.0)	1 (5.0)	
AST/ALT	2 (10.0)	3 (15.0)	2 (10.0)	
Bilirubin	2 (10.0)		1 (5.0)	
Febrile neutropenia			10 (50.0)	1 (5.0)

cured with anthracycline-containing combination chemotherapy [5, 16, 17].

In the present study, the addition of alemtuzumab to CHOP as the first-line regimen showed a high complete response rate of 65.0%, 1-year event-free survival rate of 43.3%, and 1-year overall survival rate of 44.3% in patients with PTCLs. Although long-term follow-up is necessary for survival, these results are comparable to previous studies [5, 16–18]. For example, in a large-scale retrospective study including 288 cases of PTCLs, the complete response rate and 5-year event-free survival for PTCLs were 54 and 33%, respectively [16]. Also, a previous study by the current authors, which adapted CHOP plus etoposide and gemcitabine for the treatment of PTCLs, produced a complete response rate of 57.7% and 1-year event-free survival rate of 50% [18]. Since there were two treatment-related deaths and one unknown cause of death in the current study, the survival rates may not be better, despite the high complete response rate.

However, the major toxicity in the current study was a high rate of opportunistic infection, with two patients dying from infectious complications. Alemtuzumab is known to contribute to immunosuppression, mainly by depleting the normal CD4 and CD8 T lymphocytes [19, 20], and an increased risk of infectious complications during alemtuzumab therapy has been previously observed with other T-cell malignancies, such as T-PLL and MF/SS [11, 12]. Enblad et al. [13] also reported that alemtuzumab monotherapy (30 mg intravenously three times a week for a maximum of 12 weeks) for patients with advanced PTCLs demonstrated promising antitumor activity, although accompanied by a high rate of severe infectious complications, with 5 out of 14 patients dying from infections. However, they suggested that far-advanced T-cell lymphomas, in combination with previous treatment, may cause severe immunosuppression even before the initiation of alemtuzumab therapy. Yet, even though the patients included in the present study were newly diagnosed and the dose of alemtuzumab was reduced to 30 mg per 3 weeks, the addition of alemtuzumab to CHOP still caused serious infectious complications.

Despite the prophylaxis of an antiviral agent, CMV reactivation or disease is already known from previous studies to be one of the serious complications of alemtuzumab therapy [13, 20]. Also, in the present study, five patients (25%) experienced CMV reactivation, while three patients developed CMV diseases, such as pneumonitis or retinitis. Although ganciclovir and/or foscarnet treatment was employed, one patient died of pneumonitis and another had a sequela of retinitis. Since acyclovir was used instead of valacyclovir for the prophylaxis of CMV, due to economic reasons, this may have increased the rates of CMV reactivation and infection in the current study. However, the rate of CMV reactivation was also high in previous studies using a valacyclovir prophylaxis [10, 12, 13]. Given these results, more frequent, such as weekly, CMV monitoring by quantitative molecular method and early preemptive treatment for CMV reactivation are needed to reduce CMV-related complications.

Cytopenia is another major toxicity related to alemtuzumab, and in the current study, most patients (90.0%) experienced grade-4 neutropenia, while 11 patients (55.0%) were hospitalized due to febrile neutropenia. Although, all cases were treated with G-CSF and antibiotics, one patient died of pneumonia. Furthermore, the dose was reduced in 11 patients (55.0%) and treatment was delayed in eight patients (40.0%) due to hematologic toxicity. These hematologic toxicities were more pronounced than in the previous study by the current authors using CHOP plus etoposide and gemcitabine [18]. However, among six patients who received prophylactic G-CSF treatment after grade-4 neutropenia or febrile neutropenia, only one patient developed same neutropenia in the subsequent cycles. Thus, routine G-CSF prophylaxis for all patients might prevent the development of severe neutropenia in the current study.

When taking the adverse infectious and hematologic events into account, the current study was closed after 20 of the planned 43 patients had been enrolled. The safety evaluation demonstrated that two patients died from serious adverse events considered to be causally related to the study drugs.

In conclusion, the alemtuzumab plus CHOP chemotherapy seemed to produce active antitumor activity in terms of the complete response rates in patients with PTCLs. However, since high infectious and hematologic toxicities were observed, careful monitoring and early treatment to prevent treatment-related mortality are needed. Alternatively, lower dosages or a different schedule of alemtuzumab could be explored to improve the safety of an alemtuzumab plus CHOP therapy. For further investigation of the role of alemtuzumab in the treatment of PTCLs, a larger-scale phase II or phase III study is warranted.

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