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ORIGINAL ARTICLE

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# CHOP plus etoposide and gemcitabine (CHOP-EG) as front-line chemotherapy for patients with peripheral T cell lymphomas

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**Abstract** *Objective*: The present study evaluated the feasibility of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) plus etoposide and gemcitabine (CHOP-EG) as front-line chemotherapy in patients with peripheral T cell lymphomas (PTCLs). *Patients and methods*: Twenty-six patients with newly diagnosed PTCLs were enrolled into the pilot study. Treatment consisted of classical CHOP plus etoposide 100 mg/m$^2$ intravenously (i.v.) on day 1 and gemcitabine 600 mg/m$^2$ i.v. on day 1 in a 3 week interval. *Results*: Fifteen complete responses (CR, 57.7%) or one unconfirmed complete response (uCR, 3.8%) and four partial responses (PR, 15.4%) were confirmed, giving an overall response rate of 76.9% (95% CI, 58.3–96.3%). Median survival has not yet been reached, while median event free survival was 215 days at a median follow-up duration of 383 days. Estimated overall survival at 1 year was 69.6%. The most severe haematological adverse event was neutropaenia, which occurred with a grade 4 intensity in 14 patients (53.8%). Additionally, febrile neutropaenia was observed in four patients (15.4%). However, there was no treatment-related death. *Conclusion*: The CHOP-EG regimen was found to be feasible in patients with PTCLs. For further investigation on the role of gemcitabine in the treatment of PTCLs, a more large scale phase II or phase III study is warranted.

**Keywords** Peripheral T cell lymphoma · CHOP · Etoposide · Gemcitabine

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## Introduction

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

Peripheral T cell lymphomas (PTCLs), as originally described in the REAL classification [4], are uncommon subsets of lymphoma and have generally poor prognosis [5]. In contrast to B cell NHL where major therapeutic advances with rituximab, a monoclonal anti-CD 20 antibody, have been recently made [6, 7], the treatment of PTCLs remains a challenge.

Etoposide has already been reported to be an active agent in the treatment of aggressive NHL [8, 9]. In a first-line therapy, a phase II study with CHOP plus etoposide regimen showed 93% of response rate and 43 months of median survival [8]. Gemcitabine (difluorodeoxycytidine) is a pyrimidine antimetabolite that has broad spectrum in solid tumors such as pancreatic, lung, bladder, and breast carcinoma, and it also has been found to have significant activity for refractory or relapsed B or T cell NHL [10, 11].

Accordingly, the present pilot study was conducted to evaluate the feasibility of CHOP plus etoposide and gemcitabine as front-line chemotherapy for patients with PTCLs.

## Patients and methods

### Eligibility criteria

Patients who entered onto this study were required to fulfill the following eligibility criteria: (1) newly diagnosed PTCLs except cutaneous T cell lymphoma and anaplastic lymphoma kinase (ALK) positive anaplastic large cell lymphoma; (2) age between 17 and 75 years; (3) Eastern Cooperative Oncology Group Scale performance status of 3 or less; (4) at least one measurable lesion; (5) adequate function of bone marrow (WBC count ≥4,000/μl and platelet count ≥100,000/μl), liver (serum bilirubin level ≤ 2.0 mg/dl and serum transaminase level ≤ 2 times the upper limit of normal range, and kidney (serum creatinine level ≤ 1.5 mg/dl); (6) normal cardiac function; (7) no other severe medical conditions; (8) no other active malignancy; and (9) provision of written informed consent.

### Patient evaluation

All the cases were reviewed by an expert haematopathologist for diagnostic confirmation and classified according to the WHO classification. Pretreatment evaluation comprised complete blood cell counts, routine chemistry measurement including serum lactate dehydrogenase (LDH), 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 the 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 sites of disease, and LDH.

### Treatment schedule

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 days 1–5) plus etoposide 100 mg/m$^2$ intravenously (i.v.) on day 1 and gemcitabine 600 mg/m$^2$ i.v. on day 1 in a 3 week interval. Patients with low or low-intermediate risk IPI were planned to receive six courses of chemotherapy followed by radiotherapy to bulky sites. Autologous stem cell transplantation (SCT) after completion of chemotherapy for patients with high or high-intermediate risk IPI was permitted. Chemotherapy was withheld for 1 week until the neutrophil count was higher than $1.5\times10^3$/μl and the platelet count more than $100\times10^9$/l. If febrile neutropaenia or grade 4 neutropaenia lasting over 7 days occurred, the starting dose of cyclophosphamide, doxorubicin, etoposide, and gemcitabine was reduced by 25% in the subsequent course of treatment.

### Definition of response and toxicity

The patient response was evaluated after every two courses of treatment and 1 month after completion of treatment according to the NHL response criteria [12], and toxicity was evaluated and graded according to the National Cancer Institute Common Toxicity Criteria (NCI CTC) version 3.0 grading system.

### Statistical analysis

All efficacy 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 and event-free survival was calculated from the study entry until treatment failure (disease progression, relapse, or death by any cause). Overall survival curves were plotted using the Kaplan–Meier method. The statistical data were obtained using the SPSS software package (SPSS 11.0 Inc. Chicago, IL, USA).

## Results

### Patient characteristics

Twenty-six patients were enrolled between May 2003 and August 2004 from three medical centers in Korea. The characteristics of the patients are summarized in Table 1. Peripheral T cell lymphoma, unspecified (53.8%) was the most common histological subtype, while eight (30.8%) patients were diagnosed with extranodal NK/T cell lymphomas. Sixteen patients (61.5%) had Ann Arbor stage III or IV disease at diagnosis and 11 (42.3%) patients were classified as high-intermediate or high risk according to the IPI scoring system.

### Response to treatment

All the patients were assessable for response. Fifteen complete responses (CR, 57.7%) or one unconfirmed complete response (uCR, 3.8%) and four partial responses (PR, 15.4%) were confirmed, giving an overall response rate of 76.9% (95% CI, 58.3–96.3%) (Table 2). Responses according to histologic subtype are also summarized in Table 3. Autologous SCT as a consolidation therapy was performed in one patient. Among 12 patients who relapsed or progressed during the study, 10 patients received salvage treatment (seven DHAP, one ICE chemotherapy followed by autologous SCT, 2 allogeneic SCT). Eight patients had died at the time of the present evaluation. Seven out of eight deaths were due to disease progression, and one patient died of pneumonia during allogeneic SCT. Median survival has not yet been reached, while median event free survival was 215 days at a median follow-up duration of

**Table 1** Characteristics of patients

| Characteristic | Number of patients (%) |
|---|---|
| Age (years) | |
| Median | 57.5 |
| Range | 20–68 |
| Gender | |
| Male | 13 (50.0) |
| Female | 13 (50.0) |
| ECOG performance status | |
| 0–1 | 23 (88.5) |
| 2–3 | 3 (11.5) |
| Histologic subtype | |
| Peripheral T cell, unspecified | 14 (53.8) |
| Extranodal NK/T cell, nasal type | 8 (30.8) |
| Angioimmunoblastic T cell | 2 (7.7) |
| ALK negative anaplastic large cell | 2 (7.7) |
| Stages | |
| I–II | 10 (38.5) |
| III–IV | 16 (61.5) |
| International prognostic index | |
| Low | 8 (30.7) |
| Low–intermediate | 7 (26.9) |
| High–intermediate | 7 (26.9) |
| High | 4 (15.4) |

383 days (range, 88–702 days) (Fig. 1a). The estimated event free survival and overall survival at 1 year was 50.0% ± 10.6% and 69.6 ± 9.6%, respectively (Fig. 1).

## Toxicity

A total of 104 cycles (median 4, range 1–6 cycles) were administrated in 26 patients assessable for toxicity. The most severe haematological adverse event was neutropaenia, which occurred with a grade 4 intensity in 14 patients (53.8%) (Table 4). Febrile neutropaenia was also observed in four patients (15.4%). However, all the cases were successfully treated with antibiotics and G-CSF and there was no treatment-related death. Nausea and stomatitis were common non-haematological toxicities. Grade 1/2 nausea and stomatitis was observed in 61.5–30.8% of patients, respectively. Yet, no grade 4 non-haematological toxicity was observed. The dose was reduced in five patients (19.2%) due to haematological toxicity.

**Table 2** Response to treatment

| Response | No. (%) |
|---|---|
| Complete response | 15 (57.7) |
| Unconfirmed complete response | 1 (3.8) |
| Partial response | 4 (15.4) |
| Stable disease | 3 (11.5) |
| Progressive disease | 3 (11.5) |

**Table 3** Response according to histologic subtype

| Histologic subtype (number) | Response (%) | | | |
|---|---|---|---|---|
| | CR/uCR | PR | SD | PD |
| Peripheral T cell, unspecified (14) | 8 (57.1) | 2 (14.3) | 3 (21.4) | 1 (7.1) |
| Extranodal NK/T cell, nasal type (8) | 5 (62.5) | 2 (25.0) | | 1 (12.5) |
| Angioimmunoblastic T cell (2) | 1 (50.0) | | | 1 (50.0) |
| ALK negative anaplastic large cell (2) | 2 (100) | | | |

*CR*, complete response; *uCR*, unconfirmed CR; *PR*, partial response; *SD*, stable disease; *PD*, progressive disease

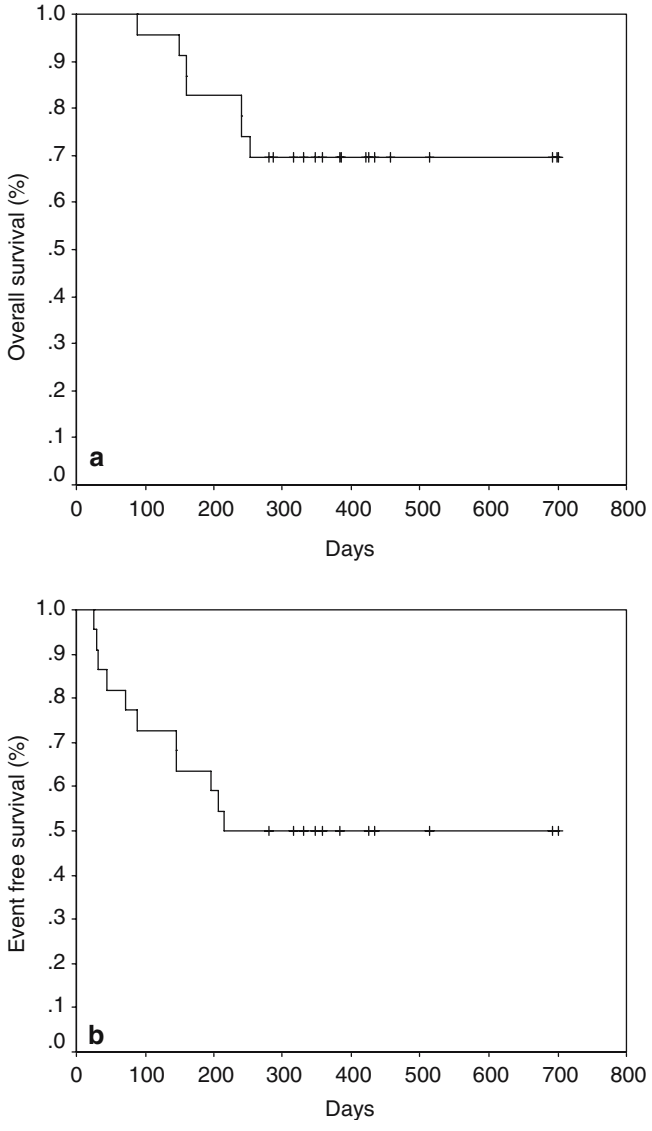


**Fig. 1** Survival curves. **a** estimated 1-year overall survival rate and **b** event free survival rate for all patients was 69.6 and 50.0%, respectively

**Table 4** Adverse reactions

| | NCI-CTC grade: no. (%) of patients ($n=26$) | | | |
|---|---|---|---|---|
| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
| Haematologic | | | | |
| Anaemia | 8 (30.8) | 3 (11.5) | | |
| Leukopaenia | 4 (15.4) | 7 (26.9) | 4 (15.4) | 11 (42.3) |
| Neutropaenia | 4 (15.4) | 5 (19.2) | 3 (11.5) | 14 (53.8) |
| Thrombocytopaenia | 4 (15.4) | 6 (23.1) | 3 (11.5) | |
| Non-heamatologic | | | | |
| Nausea | 12 (46.2) | 5 (19.2) | | |
| Stomatitis | 8 (30.8) | 3 (11.5) | 1 (3.8) | |
| Diarrhoea | 4 (15.4) | 2 (7.7) | | |
| Constipation | 5 (19.2) | 2 (7.7) | 1 (3.8) | |
| Neuropathy | 3 (11.5) | 2 (7.7) | | |
| Febrile neutropaenia | | | 3 (11.5) | 1 (3.8) |
| Infection without neutropaenia | | 2 (7.7) | 1 (3.8) | |

## Discussion

PTCLs are clinically aggressive and have a worse prognosis than high-grade B-cell lymphomas. Fewer than 30% of the patients are expected to be cured with anthracycline-containing combination chemotherapy [5, 13].

In the present study, the addition of gemcitabine to CHOP plus etoposide as first-line regimen showed a high complete response rate of 61.5%, 1 year event-free survival rate of 50.0%, and 1 year overall survival rate of 69.6% in patients with PTCLs. Although long-term follow-up is necessary for survival, these results are comparable to previous studies [5, 13, 14]. For example, in a large-scale retrospective study including 68 cases of PTCLs, the complete response rate and the 5 year failure-free survival for PTCLs was 65 and 38%, respectively [5]. Recently, the survival benefit of CHOP plus etoposide compared with CHOP alone has already been demonstrated for young patients with good prognosis aggressive lymphomas in a randomized trial, while subgroup analysis according to immunophenotype was not performed [15]. The efficacy of gemcitabine as a monotherapy for advanced PTCLs was also shown in the previous clinical studies [11, 16]. Moreover, gemcitabine plus dexamethasone and cisplatin regimen was recently found to be active and tolerable in a salvage setting for the patients with B-cell NHL [10].

Gemcitabine is an analogue of cytosine arabinoside, one of the active agents for lymphoma, but is more effectively taken up into cells, phosphorylated, and retained intracellulary [17]. It also has a self-potentiating mechanism of action, resulting in enhanced accumulation and prolonged retention within malignant cells [18]. These properties may allow gemcitabine to be a more effective antilymphoma agent. Considering that drug resistance is an important cause of treatment failure, the addition of gemcitabine to conventional regimen might be a challenge to improve the poor outcome of PTCLs.

One of the major toxicities related to gemcitabine is myelosuppression. In the current study, 14 patients (53.8%) experienced grade 4 neutropaenia and four patients (15.4%) were hospitalized due to febrile neutropaenia. However, all the cases were successfully treated and there was no treatment-related death.

In conclusion, the CHOP-EG regimen was found to be feasible in patients with PTCLs. For further investigation on the role of gemcitabine in the treatment of PTCLs, a more large scale phase II or phase III study is warranted.

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