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ORIGINAL REPORT

Phase II Study of SMILE Chemotherapy for Newly Diagnosed Stage IV, Relapsed, or Refractory Extranodal Natural Killer (NK)/T-Cell Lymphoma, Nasal Type: The NK-Cell Tumor Study Group Study

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ABSTRACT

Purpose
To explore a more effective treatment for newly diagnosed stage IV, relapsed, or refractory extranodal natural killer/T-cell lymphoma, nasal type (ENKL), we conducted a phase II study of the steroid (dexamethasone), methotrexate, ifosfamide, L-asparaginase, and etoposide (SMILE) regimen.

Patients and Methods
Patients with newly diagnosed stage IV, relapsed, or refractory disease and a performance status of 0 to 2 were eligible. Two cycles of SMILE chemotherapy were administered as the protocol treatment. The primary end point was the overall response rate (ORR) after the protocol treatment.

Results
A total of 38 eligible patients were enrolled. The median age was 47 years (range, 16 to 67 years), and the male:female ratio was 21:17. The disease status was newly diagnosed stage IV in 20 patients, first relapse in 14 patients, and primary refractory in four patients. The eligibility was revised to include lymphocyte counts of 500/μL or more because the first two patients died from infections. No treatment-related deaths were observed after the revision. The ORR and complete response rate after two cycles of SMILE chemotherapy were 79% (90% CI, 65% to 89%) and 45%, respectively. In the 28 patients who completed the protocol treatment, 19 underwent hematopoietic stem-cell transplantation. The 1-year overall survival rate was 55% (95% CI, 38% to 69%). Grade 4 neutropenia was observed in 92% of the patients. The most common grade 3 or 4 nonhematologic complication was infection (61%).

Conclusion
SMILE chemotherapy is an effective treatment for newly diagnosed stage IV, relapsed or refractory ENKL. Myelosuppression and infection during the treatment should be carefully managed.

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INTRODUCTION

Extranodal natural killer (NK)/T-cell lymphoma, nasal type (ENKL), is a lymphoma associated with the Epstein-Barr virus (EBV), which is much more common in Asia and Latin America than in Western countries.[1,2] More than two thirds of patients with ENKL have stage I or II disease in the upper aerodigestive tract.[3-6] The prognosis for localized ENKL has been improving as a result of the use of either concurrent chemoradiotherapy[7,8] or chemotherapy with sandwiched radiotherapy.[9] In contrast, most patients with newly diagnosed stage IV, relapsed, or refractory ENKL treated with conventional chemotherapy designed for aggressive lymphomas, such as cyclophosphamide, doxorubicin, vincristine, and prednisone, survive for less than a year.[6] The poor outcome is partly because ENKL tumor cells express P-glycoprotein, which results in tumor multidrug resistance.[10-12] There are a number of long-term survivors among patients with advanced-stage, relapsed, or refractory ENKL who have undergone hematopoietic stem-cell transplantation (HSCT).[13-15] However, patients who received HSCT in complete response (CR) showed better prognosis than those who received HSCT during non CR. Therefore, the development of an effective chemotherapy for these patients is an important initial step in improving treatment outcomes.

Table 1. SMILE Chemotherapy

Agent	Dose/d	Route	Day
Methotrexate	2 g/m^2*	IV (6 hours)	1
Leucovorin	15 mg × 4	IV or PO	2, 3, 4
Ifosfamide	1,500 mg/m^2	IV	2, 3, 4
Mesna	300 mg/m^2 × 3	IV	2, 3, 4
Dexamethasone	40 mg/d	IV or PO	2, 3, 4
Etoposide	100 mg/m^2*	IV	2, 3, 4
L-asparaginase (*Escherichia coli*)	6,000 U/m^2	IV	8, 10, 12, 14, 16, 18, 20
G-CSF		SC or IV	Day 6 to WBC > 5,000/μL

NOTE. Cycles were repeated every 28 days. Two courses were planned as the protocol treatment.
Abbreviations: G-CSF, granulocyte-colony stimulating factor; IV, intravenously; PO, orally; SC, subcutaneous injection; SMILE, steroid (dexamethasone), methotrexate, ifosfamide, L-asparaginase, and etoposide.
*The recommended dose was determined in the preceding phase I study.

To explore the possibility of more effective induction chemotherapy for NK-cell neoplasms, the NK-Cell Tumor Study Group, comprising Japanese and Asian hematologists, has formulated a novel chemotherapeutic regimen: steroid (dexamethasone), methotrexate, ifosfamide, L-asparaginase, and etoposide (SMILE). These agents are multidrug resistance independent and may be key drugs for NK-cell neoplasms or for EBV-associated disease. From the phase I trial of SMILE, the recommended doses of methotrexate and etoposide were determined.[16] The CR rate in the phase I trial was 50% (three of six eligible patients), and the overall response rate (ORR) was 67% (four of six patients). To further evaluate the efficacy of SMILE chemotherapy, we conducted a subsequent phase II study.

PATIENTS AND METHODS

Eligibility Criteria

Patients with newly diagnosed stage IV, relapsed, or refractory disease who had undergone first-line chemotherapy were eligible. Those with aggressive NK-cell leukemia were excluded because no patients with aggressive NK-cell leukemia had been enrolled in the prior phase I study.[16] Patients who had received autologous HSCT more than 12 months before registration were also eligible. The other inclusion and exclusion criteria for the study were the same as those for the prior phase I study.[16] Briefly, patients from 15 to 69 years of age with a performance status of 0 to 2, based on the Eastern Cooperative Oncology Group scale, and preserved organ functions were included. Neither chemotherapy nor radiotherapy was administered within 21 days before registration. Patients who had clinical symptoms of CNS involvement were excluded.

The pretreatment staging procedures included a physical examination, a bone marrow aspiration and/or biopsy, a chest radiograph, and a computed tomography scan of the nasal cavity, neck, chest, abdomen, and pelvis. An endoscopy of the upper gastrointestinal tract and a positron emission tomography scan were recommended but not mandatory.

After patient enrollment, hematoxylin-eosin–stained sections were histologically reviewed by the Central Pathology Review Board based on the WHO classification.[1] Immunohistochemical staining was performed at the central pathology office using formalin-fixed, paraffin-embedded sections with antibodies against CD3, CD20, CD56, perforin, and granzyme B. In addition, in situ hybridization for EBV-encoded small RNA-1 was performed.

Registration of patients was conducted by facsimile between the participating physicians and the Center for Supporting Hematology-Oncology Trials Data Center (Nagoya, Japan). The study was approved by both the protocol review committee and the institutional review board of each institution. Written informed consent was obtained from all of the patients. The study was registered to the University Hospital Medical Information Network Clinical Trials Registry.

Treatment

SMILE chemotherapy was administrated as indicated in Table 1. On the basis of the results of the phase I trial,[16] administration of granulocyte colony-stimulating factor was mandatory from day 6 and discontinued if the leukocyte count exceeded 5,000/μL after the nadir phase. Antibiotic prophylaxis of sulfamethoxazole-trimethoprim was recommended. The criteria for the initiation of a second course of SMILE were as follows (1): a total of 4 weeks or more had passed since the prior course; (2) all of the following were achieved at least 1 day before the second course of SMILE: a leukocyte count of $\geq$ 2,000/μL, a platelet count of $\geq$ 100,000/μL, AST and ALT levels $\leq$ 5× the upper limit of normal, total bilirubin of $\leq$ 2.0 mg/dL, or serum creatinine of $\leq$ 1.5 mg/dL; and (3) there were no other symptoms or complications that were not suitable for the initiation of a second course. If there was no recovery 4 weeks after the day of the scheduled second course, the protocol treatment was terminated. Two courses of SMILE chemotherapy were planned for the protocol treatment. After the planned two courses, patients could undergo additional courses of SMILE and/or other chemotherapy, with or without autologous/allogeneic HSCT. The decision was made according to the discretion of treating physicians mainly on the basis of the patient's age, conditions, and the availability of HSC donors.

Response and Toxicity Criteria

The responses were assessed by the Central Imaging Review Board according to criteria modified from the WHO response criteria[17] that were also used in the prior phase I study of SMILE chemotherapy.[16] All of the examinations for restaging were done within 4 to 6 weeks (from day 22 to day 42) of the second course of SMILE. Because ENKL frequently occurs in the nasal/paranasal sites and leaves scar or necrotic tissue, it is sometimes difficult to determine whether or not a patient strictly attains CR using the WHO response criteria[17] or the International Workshop criteria.[18] Therefore, in this trial, CR was defined as the complete disappearance of all objective signs of disease, including enlarged lymph nodes or hepatomegaly and splenomegaly at the restaging. Partial response (PR) was defined as at least a 50% reduction of tumor volume without the occurrence of new lesions at the restaging. Progressive disease was defined as a greater than 25% increase in the sum of tumor lesions or the emergence of one or more new lesion(s) or clinical symptoms that indicate disease progression, such as "B" symptoms or elevated serum lactate dehydrogenase levels. No response was defined as any response that did not fall into the other defined categories. If a patient died before day 42 of the second course of SMILE and could not undergo the defined restaging procedure, the patient's response was recorded as early death. The ORR rate was defined as the proportion of all patients who were able to be evaluated for response who experienced CR or PR.

Toxicity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. In cases of grade 4 thrombocytopenia,

doses of methotrexate, ifosfamide, and etoposide were reduced to two thirds of their previous levels in the second course. L-asparaginase was discontinued if it induced grades 3 or 4 allergic reactions/hypersensitivity, pancreatitis, or hypotension. If L-asparaginase induced grades 1 or 2 allergic reactions/hypersensitivity, the dose of L-asparaginase was reduced by half. In this case, the use of prednisone at a dose of 1 mg/kg/d was permitted. L-asparaginase was stopped if grade 4 thrombocytopenia or grade 3 nonhematologic toxicity was observed. In the cases for which the first course of L-asparaginase was discontinued, L-asparaginase was readministered if the patient recovered from grade 4 thrombocytopenia or grade 3 nonhematologic toxicity. If the concentration of methotrexate exceeded 1×10^{-7} mol/L 72 hours after the administration during the first course, the dose of methotrexate in the second course was reduced to two thirds.

Statistical Analysis

The primary end point was an ORR after two courses of SMILE chemotherapy. The secondary end points were CR rate after two courses of SMILE chemotherapy, 1-year overall survival (OS), response of the subgroup, or toxicity. The expected ORR was estimated to be 60%, and the threshold ORR was estimated to be 35%, on the basis of our previous observations.[6,19] With a statistical power of 80% and a one-sided, type I error of 5%, the number of eligible patients required for this study was calculated to be 25 using a binomial analysis method. The projected sample size was 28 patients, with an accrual of 3 years and the expectation that 10% of patients would be deemed ineligible.

OS was defined as the time from registration until death from any cause or until the date of the last follow-up for the patients who survived. Survival estimates were calculated using the Kaplan-Meier method, and the hazard ratio (HR) was estimated using a Cox regression. All analyses were performed using STATA SE 10 software (STATA, College Station, TX).

RESULTS

Patient Characteristics

As a result of an excellent accrual, the study protocol was revised to increase the statistical power from 80% to 90% in March 2009. The projected number of patients for this study was increased from 28 to 38. Ultimately, 39 patients were enrolled from 19 institutions between July 2007 and October 2009. Histologic diagnosis of all patients except one was confirmed as ENKL by the Central Pathology Review Board. The single patient who was excluded from further analyses was judged to have CD56-positive rhabdomyosarcoma by the Central Pathology Review Board.

The baseline characteristics of 38 eligible patients are listed in Table 2. The median age was 47 years (range, 16 to 67 years), and the male:female ratio was 21:17. Twenty patients (53%) had newly diagnosed stage IV disease, 14 were in first relapse, and four were in primary refractory state. Two patients were treated with radiation alone as the initial therapy. Among the 16 patients who received chemotherapy as their first-line therapy, five patients were treated with anthracycline-containing chemotherapies, and 13 patients were treated with platinum-based regimens. Two patients were treated with chemotherapy containing both anthracycline and platinum.

Table 2. Baseline Patient Characteristics (N = 38)

Characteristic	No. of Patients	%
Age, years		
Median	47	
Range	16 to 67	
Sex		
Male	21	55
Female	17	45
Site(s) of involvement at diagnosis		
Upper aerodigestive tract	35	92
Extra-upper aerodigestive tract only	3	8
Disease state		
Newly diagnosed stage IV	20	53
First relapse	14	37
Refractory to the first-line treatment	4	11
Stage at enrollment		
IE or IIE	11	29
IIIE or IV	27	71
"B" symptoms present	18	47
Elevated serum LDH	16	42
Performance status		
0	21	55
1	12	32
2	5	13
Prior treatment		
None	20	53
Radiotherapy alone	2	5
Chemotherapy alone	3	8
Concurrent chemoradiotherapy	9	24
RT-DeVIC	6	
CCRT-VIPD or VIDL	2	
RT-CHOP	1	
Other combined modality therapies	4	11

Abbreviations: CCRT, concurrent chemoradiotherapy; DeVIC, dexamethasone, etoposide, ifosfamide, and carboplatin; LDH, lactate dehydrogenase; VIDL, etoposide, ifosfamide, dexamethasone, and L-asparaginase; VIPD, etoposide, ifosfamide, cisplatin, and dexamethasone.

Treatment

Twenty-eight patients (74%) completed the planned treatment. In two patients, the treatment was discontinued on day 4 because of methotrexate-associated encephalopathy and intestinal perforation owing to rapid tumor lysis. L-asparaginase was discontinued in four patients due to adverse events (AEs), including two patients with allergy to L-asparaginase (both in the second course), one patient with pancreatitis (grade 2, in the first course), and one patient with liver function derangement (in the first course). In two of these four patients, L-asparaginase was readministered at a 50% dose reduction. One allergic patient received simultaneously prednisolone 1 mg/kg. In another four patients, L-asparaginase was also stopped per protocol, owing to AEs of preceding agents (methotrexate, ifosfamide, and etoposide), including two patients with infections and two patients with thrombocytopenia. The relative dose-intensity of L-asparaginase in the first course of SMILE was 81%. Two of these eight patients who had L-asparaginase discontinued achieved CR. The relative dose-intensity of CR patients was 92%.

Additional courses of SMILE were given for 21 patients (one course, 10 patients; two courses, three patients; three courses, two patients; four courses, six patients). The median number of courses of SMILE administered was three (range, one to six courses). Treatment of the 28 patients who completed two courses of SMILE were as follows: chemotherapy only (n = 7), autologous HSCT (n = 4), or allogeneic HSCT (n = 17; myeloablative, n = 15, nonmyeloablative, n = 2). No difficulties in mobilizing peripheral blood HSC were encountered in the four patients who received autologous HSCT. Among the seven patients who did not complete the protocol treatment, two of them received no additional treatment and died as a

Table 3. Incidence and Maximum Severity of Adverse Events (N = 38)

Adverse Event	Grade 3 No.	Grade 3 %	Grade 4 No.	Grade 4 %
Hematologic				
Leukopenia	9	24	29	76
Neutropenia	3	8	35	92
Anemia	18	47	1	3
Thrombocytopenia	9	24	15	40
Nonhematologic				
Hypofibrinogenemia	4	11	0	0
APTT elongation	4	11	0	0
Hypoalbuminemia	6	16	0	0
Hyperbilirubinemia	3	8	1	3
AST elevation	12	32	0	0
ALT elevation	10	26	2	6
Creatinine	2	5	0	0
Hyponatremia	11	29	1*	3
Hyperglycemia	7	18	0	0
Amylase	6	16	1*	3
Appetite loss	8	21	1*	3
Diarrhea	4	11	0	0
Nausea	5	13	0	0
Mucositis	5	13	0	0
Vomiting	2	5	0	0
Infection	17	45	6†	16
Somnolence	1	3	2	5
Encephalopathy	0	0	1	3

NOTE. Grade 3 hypernatremia, allergic reaction, fever, and dehydration were observed in one patient each.
Abbreviation: APTT, activated partial thromboplastin time.
*Related to grade 2 pancreatitis in one patient.
†Including the two patients who died as a result of infection (two treatment-related deaths).

result of disease. Three patients were treated with other chemotherapy, and two of them underwent allogeneic HSCT without response.

Toxicity

Table 3 lists all grade 3 or 4 AEs that occurred in the 38 eligible patients who were enrolled onto this trial. After the death of initial two patients from grade 5 infections (patients 1 and 2; see Appendix, online only), the protocol was revised to include a careful assessment of infection and the incorporation of a lymphocyte count of $\geq 500/\mu L$ into the eligibility criteria. There were no subsequent treatment-related deaths.

Grade 4 neutropenia was common (92%). The nonhematologic grade 4 toxicities included infection (n = 6), hyperbilirubinemia (n = 1), ALT elevation (n = 2), and encephalopathy (n = 1); two patients experienced grade 4 somnolence, which was complicated by a grade 3 infection in one patient and by grade 4 encephalopathy in the other patient. One patient experienced grade 2 pancreatitis and had complications from grade 4 hyponatremia, hyperamylasemia, and appetite loss. The most common grade 3 nonhematologic AE was infection (45%). Allergic reactions due to L-asparaginase of any grade were observed in five patients (three with grade 1, one with grade 2, and one with grade 3). The toxic profiles according to disease status at the time of study entry (newly diagnosed/relapsed/refractory) are shown in Appendix Table A1 (online only). The grade 4 hematologic toxicity rates of newly diagnosed and relapsed patients were 95% and 93%, respectively. The grade 4 nonhematologic toxicity rates of newly diagnosed and relapsed patients were 35% and 14%, respectively. None of these differences were statistically significant ($P = .99$ and $P = .25$). No clinical predictors of toxicity were found. Only hyponatremia was associated with newly diagnosed and refractory diseases.

Table 4. Response After Two Cycles of SMILE Chemotherapy (N = 38)

Response	All Patients (N = 38) No.	All Patients (N = 38) %	Newly Diagnosed Stage IV (n = 20) No.	Newly Diagnosed Stage IV (n = 20) %	First Relapse (n = 14) No.	First Relapse (n = 14) %	Refractory to the First-Line Therapy (n = 4) No.	Refractory to the First-Line Therapy (n = 4) %
CR	17	45	8	40	9	64	0	0
PR	13	34	8	40	4	29	1	25
NR	1	3	1	5	0	0	0	0
PD	4	10	1	5	1	7	2	50
ED	3	8	2	10	0	0	1	25

Abbreviations: CR, complete response; ED, early death; NR, no response; PD, progressive disease; PR, partial response; SMILE, steroid (dexamethasone), methotrexate, ifosfamide, L-asparaginase, and etoposide.

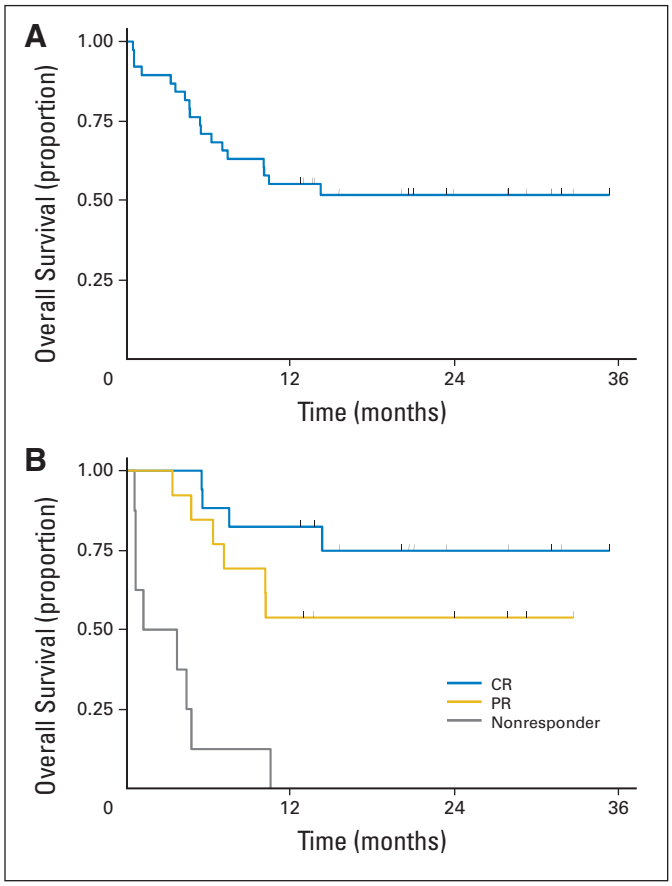

Fig 1. Kaplan-Meier estimates of overall survival (OS) of patients treated with steroid (dexamethasone), methotrexate, ifosfamide, L-asparaginase, and etoposide chemotherapy. (A) The 1-year OS of 38 patients was 55% (95% CI, 38% to 69%). The median follow-up of survivors was 24 months (range, 13 to 35 months). (B) The 1-year OS was 82% (95% CI, 55% to 94%) for patients who attained complete response (CR) and 54% (95% CI, 25% to 76%) for those who attained partial response (PR).

Efficacy and Survival

Among the 38 eligible patients, the response was CR in 17 patients (45%), PR in 13 patients, no response in one patient, progressive disease in four patients, and early death in three patients (Table 4). The ORR was 79% (90% CI, 65% to 89%). There were no differences in either the ORR or CR rate between patients with newly diagnosed stage IV disease and those with first-relapse disease. With respect to progressive disease in four patients, one occurred during the first course of SMILE, one after the first course, and two after the completion of two courses.

The median follow-up time of the living patients was 24 months, with a range of 13 to 35 months. The OS rate at 1 year, which was one of the secondary end points, was 55% (95% CI, 38% to 69%; Fig 1A). The progression-free survival (PFS) at 1 year was 53% (95% CI, 36% to 67%). The patients who attained response with SMILE chemotherapy had a higher OS (Fig 1B). The OS and PFS by the disease state at entry are shown in Figure 2A and 2B. Patients with relapsed disease showed better 1-year OS (79%) and PFS (71%) as compared with patients with refractory disease (P = .04 and .05, respectively). The survival curves of patients (excluding early deaths; n = 35) according to the type of poststudy therapy (autologous/allogeneic HSCT/chemotherapy) are shown in Figures 2C and 2D. Patients who received autologous HSCT seemed to show better OS and PFS, but the difference was not statistically significant. Univariate analysis for OS showed that presence of B symptoms (HR, 3.1, P = .01), performance status of 1 or 2 (HR, 3.1, P = .002), elevated serum lactate dehydrogenase (HR, 6.1, P = .001), and hemoglobin of less than 12 g/dL (HR, 3.9, P = .007) were significant prognostic factors.

DISCUSSION

Our results indicate that SMILE chemotherapy is effective for the treatment of newly diagnosed stage IV, relapsed, or refractory ENKL. The ORR after two cycles of SMILE (79%; 90% CI, 65% to 89%) clearly exceeded the threshold ORR (35%).[20] The 1-year OS rate (55%) was much improved compared with the previous treatment strategy.

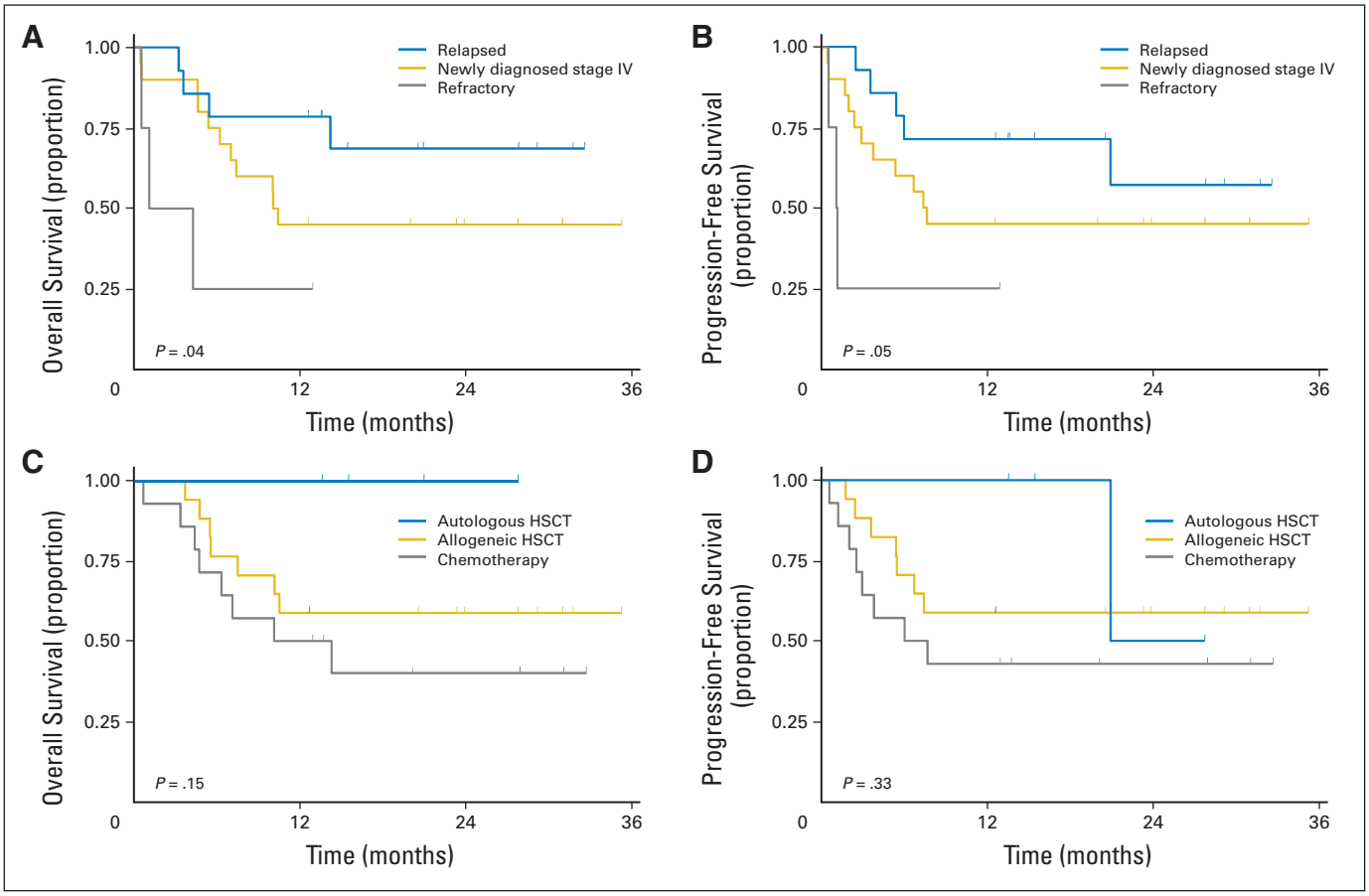

Fig 2. Kaplan-Meier estimates of overall survival (OS) and progression-free survival (PFS) of patients by the subgroup analysis. (A) OS of patients by the disease state at entry. The 1-year OS was 45% (95% CI, 23% to 65%) for patients with newly diagnosed stage IV disease, 79% (95% CI, 47% to 93%) for patients with relapsed disease, and 25% (95% CI, 1% to 67%) for patients with refractory disease. The difference was statistically significant (P = .04). (B) PFS of patients by the disease state at entry. The 1-year PFS was 45% (95% CI, 23% to 65%) for patients with newly diagnosed stage IV disease, 71% (95% CI, 41% to 88%) for patients with relapsed disease, and 25% (95% CI, 1% to 67%) for patients with refractory disease. The difference was statistically significant (P = .05). (C) OS of patients excluding early death (n = 35) by type of poststudy therapy. The 1-year OS was 100% for patients who received autologous hematopoietic stem-cell transplantation (HSCT), 59% (95% CI, 36% to 78%) for patients who received allogeneic HSCT, and 41% (95% CI, 19% to 63%) for patients treated with chemotherapy only. The difference was not statistically significant (P = .15). (D) PFS of patients excluding early death by type of poststudy therapy. The 1-year PFS was 100% for patients who received autologous HSCT, 59% (95% CI, 36% to 78%) for patients who received allogeneic HSCT, and 35% (95% CI, 14% to 57%) for patients treated with chemotherapy only. The difference was not statistically significant (P = .33).

With regard to the safety of SMILE, myelosuppression and infection should be carefully monitored during and after SMILE chemotherapy. To avoid severe AEs, the use of granulocyte colony-stimulating factor is considered mandatory, starting on day 6 and continuing until recovery beyond the nadir. In addition, full-dose administration of SMILE should be avoided for patients who are in poor condition, including those with lymphopenia less than 500/μL or large tumor burden. A lymphocyte count was added to the eligibility criteria because all three of the patients who died of neutropenic infection in the phase I and phase II SMILE studies had low lymphocyte counts before treatment. Decreased-dose SMILE[21] and less-intensive L-asparaginase chemotherapies[22-24] are candidate strategies for those patients with poor pretreatment conditions.

L-asparaginase–based chemotherapy has been highlighted as a promising treatment for ENKL. L-asparaginase was shown to induce apoptosis of ENKL cells in vitro; this result was attributed to low asparagine synthetase expression.[25] In fact, there were several case reports in the early 2000s in which ENKL showed an excellent response to L-asparaginase.[26-30] Recently, a phase II study of L-asparaginase, methotrexate, and dexamethasone (AspaMetDex) for relapsed or refractory ENKL was reported by a French group.[22] Nineteen patients were enrolled, and the CR rate was 61%. The median survival time was 12.2 months, and the 1-year OS was 45%. The AspaMetDex therapy is also promising, but there are several differences from the SMILE study. First, 53% of patients in our SMILE study had newly diagnosed stage IV ENKL which showed poor prognosis with conventional chemotherapy.[6] In contrast, the GELA (Groupe d'Etude des Lymphomes de l'Adulte)/GOELAMS (Groupe Ouest-Est des Leucémies et des Autres Maladies du Sang) study included only patients with relapsed/refractory disease. This resulted in a different ratio of patients with advanced-stage disease between the SMILE study (27 of 38 patients, 71%) and the AspaMetDex study (seven of 19 patients, 37%). Second, 17 of the 19 patients were initially treated with anthracycline-based chemotherapy in the French study. In contrast, 81% of the patients who had prior therapy in our study received platinum-based chemotherapy before SMILE, which suggests that different patient groups were selected in the two studies. Currently, these SMILE and AspaMetDex regimens are both promising for relapsed/refractory ENKL. A comparative study is required for a conclusion, but is not realistic for this type of rare lymphoma.

The optimal course of SMILE chemotherapy and the most appropriate timing of HSCT for patients after two courses of SMILE remain undetermined. In addition, the optimal treatment strategy for patients who cannot undergo HSCT needs further clinical evaluation. It has been speculated that the SMILE regimen may also be effective for T-cell lymphomas because ENKL and mature T-cell lymphomas share several clinical and pathologic features, such as extranodal predilection and expression of cytotoxic molecules. This speculation should be confirmed in further clinical studies.

In conclusion, the results of this phase II study demonstrate that two cycles of SMILE is an effective chemotherapy regimen for patients with newly diagnosed stage IV, relapsed, or refractory ENKL. However, the SMILE regimen is potentially toxic, and careful patient monitoring is needed.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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