SMILE for natural killer/T-cell lymphoma: analysis of safety and efficacy from the Asia Lymphoma Study Group

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Natural killer/T-cell lymphoma is rare and aggressive, with poor outcome. Optimal treatment remains unclear. A novel regimen dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide (SMILE) showed promise in phase 1/2 studies with restrictive recruitment criteria. To define the general applicability of SMILE, 43 newly diagnosed and 44 relapsed/refractory patients (nasal, N = 60, nonnasal, N = 21; disseminated, N = 6; male, N = 59; female, N = 28) at a median age of 51 years (23-83 years) were treated. Poor-risk factors included stage III/IV disease (56%), international prognostic index of 3 to 5 (43%), and Korean prognostic scores of 3 to 4 (41%). A median of 3 (0-6; total = 315) courses of SMILE were administered. Significant toxicities included grade 3/4 neutropenia (N = 57; 5 sepsis-related deaths); grade 3/4 thrombocytopenia (N = 36); and nephrotoxicity (N = 15; 1 acute renal failure and death). Interim analysis after 2 to 3 cycles showed complete remission rate of 56%, partial remission rate of 22%, giving an overall response rate of 78%. On treatment completion, the overall-response rate became 81% (complete remission = 66%, partial remission = 15%). Response rates were similar for newly diagnosed or relapsed/refractory patients. At a median follow-up of 31 months (1-84 months), the 5-year overall survival was 50% and 4-year disease-free-survival was 64%. Multivariate analysis showed that international prognostic index was the most significant factor impacting on outcome and survivals. (*Blood*. 2012;120(15):2973-2980)

Introduction

Extranodal natural killer (NK)/T-cell lymphoma, nasal type, is a distinct entity as defined by the World Health Organization.[1] Neoplastic cells express cytoplasmic-CD3ε, CD56, and cytotoxic molecules; but they are negative for surface-CD3. This phenotype suggests a putative NK-cell origin. Lymphoma cells are invariably infected by clonal Epstein-Barr virus (EBV). Although uncommon, these lymphomas show a peculiar geographic predilection for Asian and South American populations. They are extremely rare but also described in other populations.[1,2]

Three clinical patterns are recognized. Nasal NK/T-cell lymphomas involve the nose, nasopharynx, and the upper aero-digestive tract.[2] Nonnasal NK/T-cell lymphoma may involve any site, commonly the skin, gut, and testes. Exclusion of a nasal primary by radiologic investigations or nasopharyngeal biopsies is necessary.[2,3] Disseminated NK/T-cell lymphoma entails widespread tissue infiltration and marrow involvement, with occasionally a leukemic phase.[2,3]

Treatment results of NK/T-cell lymphoma are poor. NK cells express high concentrations of the multidrug-resistant (MDR) P-glycoprotein, so that anthracycline-containing regimens are ineffective.[4] Recently, a regimen dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide (SMILE) has been devised to tackle specifically these problems.[5] The regimen comprises 3 non–P-glycoprotein–dependent drugs dexamethasone, methotrexate, and ifosfamide. L-Asparaginase is incorporated, based on its activity in relapsed/refractory NK/T-cell lymphomas.[6] Etoposide is included, because of its efficacy in the hemophagocytic syndrome associated with NK-cell or T-cell malignancies.[7] The SMILE protocol has been tested in a multicenter phase 2 study conducted by the NK Tumor Study Group, where 38 patients with stage IV, relapsed/refractory NK/T-cell lymphomas were treated.[8] The results showed a complete remission (CR) rate of 45% and a partial remission rate (PR) of 34%, giving an overall response rate (ORR) of 79%.

In this phase 2 study,[8] patients were stringently selected for good performance status, normal neutrophil and platelet counts, adequate lymphocyte count, and normal liver and renal functions. However, patients with NK/T-cell lymphoma often present with low white cell and platelet counts and impaired liver function tests, owing either to hemophagocytic syndrome or direct infiltration.[2,3] The efficacy and safety of SMILE in an unselected patient population remain unclear, particularly for those not meeting these inclusion criteria, who in fact are the majority. Furthermore, only 2 courses of SMILE were administered according to protocol design, so that the safety of a standard 6-course treatment is undefined.

To clarify these issues, the Asia Lymphoma Study Group examined the use of SMILE in an unselected cohort of patients. The results may therefore reflect the actual safety and efficacy of SMILE when used clinically.

Methods

Patients

Patients were recruited from 3 centers (Queen Mary Hospital, Hong Kong; SamSung Medical Center, Seoul; and National Cancer Center, Singapore).

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These were patients not eligible for the phase 2 SMILE study, so that none had been included in the phase 2 SMILE study report.[8] At Queen Mary Hospital, all consecutive patients with newly diagnosed or refractory/relapsed disease at any stage (N = 44) were recruited without further exclusion criteria. At SamSung Medical Center and Singapore National Cancer Centre, all consecutive patients with stage III/IV, and relapsed/refractory diseases were recruited (N = 33 and 10, respectively). All patients gave informed consent in accordance with the Declaration of Helsinki. The protocol had been approved by the respective institution review boards.

Diagnostic evaluation

Recruitment diagnostic criteria included typical histology, expression of CD3ϵ, CD56, cytotoxic molecules, and EBV-encoded early RNA.[1] Standard staging procedures, including bilateral marrow trephine biopsies, and computed tomography of thorax and abdomen, were adopted.[2] Magnetic resonance imaging also was used for nasal lymphomas, owing to its superiority in the detection of soft tissue involvement.[2] Positron emission tomography was recommended but not compulsory.[9]

Treatment and response criteria

Details of the SMILE protocol have been published (supplemental Methods, available on the *Blood* Web site; see the Supplemental Materials link at the top of the online article).[5,8] Treatment precautions and supportive care are given in supplemental file 1. L-Asparaginase from *Escherichia coli* was used as first choice and from *Erwinia* when sensitivity occurred. Adverse effects were assessed with standard World Health Organization grading. Dose reduction with respect to adverse effects in the preceding cycle was according to published guidelines.[5,8] Responses to treatment were assessed by standard criteria.[10] If positron emission tomography/computed tomography was performed, response was assessed according to published recommendations.[11] Interim response was assessed after 2 or 3 courses. Patients achieving CR or PR continued to receive SMILE until hematopoietic stem cell transplantation (HSCT), relapse, or completion of 6 courses. Patients in interim CR and with original diseases localized to anatomic sites judged by the investigators to be amendable to irradiation received sandwiched involved-field radiotherapy before the next treatment. Patients with nonremission on interim assessment might still remain on SMILE or would receive other salvage regimens. Completion response was defined as the response at the last course of SMILE. After achievement of complete response, routine surveillance radiologic imaging was not recommended, unless clinical evidence of disease recurrence was present.

Data and survival analysis

All cases were analyzed on an intention-to-treat basis. The study period was from March 2005 to February 2012. Overall survival (OS) was defined as the time from study entry to death or last follow-up. Disease-free survival (DFS) was defined as the time from remission to relapse or death. Because a significant proportion of patients achieved CR, and PR patients invariably progressed, progression-free-survival was not evaluated in this study. Data were censored at the time of HSCT. The impact of sex, age, status (newly diagnosed vs relapsed/refractory), site of presentation (nasal vs nonnasal vs disseminated), bone marrow infiltration, leukemic involvement, increased lactate dehydrogenase, performance status, stage, international prognostic index (IPI), and Korean prognostic index on achievement of CR was studied by univariate analysis. Significant factors on univariate analysis were further examined by multivariate analysis with logistic regression. Analysis of survivals (OS, DFS) was conducted by the Kaplan-Meier method. Potential prognostic factors (as for CR) also were analyzed for their impact on survivals. Cox regression analysis with the forward stepwise method was used for multivariate analysis of factors impacting on survivals. Two-tailed *P* values of less than .05 were taken as significant. All tests were performed with the SPSS 15.0 software package (SPSS).

Results

Patients

Fifty-nine men and 28 women, at a median age of 51 years (23-83 years) were treated. Ethnicities were Chinese (N = 52), Korean (N = 33), Japanese (N = 1), and Nepalese (N = 1). Ten of these patients had very briefly been reported previously.[12] There were 43 newly diagnosed and 44 relapsed/refractory patients. For relapsed/refractory patients, previous treatments included anthracycline-containing regimens (cyclophosphamide, doxorubicin, vincristine, prednisolone [CHOP]; or CHOP-like regimens) alone (N = 30), anthracycline-containing chemotherapy (CHOP or CHOP-like regimens) followed by radiotherapy (N = 7), concomitant chemotherapy and radiotherapy[13] (N = 5), and radiotherapy alone (N = 2). The median number of cycles of previous chemotherapy was 6 (0-7) Newly diagnosed patients were comparable with relapsed/refractory patients in clinicopathologic parameters (Table 1). Conventional unfavorable factors for the cohort included marrow involvement (24%), systemic dissemination (37%), increased lactate dehydrogenase (55%), hypoalbuminemia (59%), stage III/IV disease (56%), high IPI of 3 to 5 (43%), and high Korean prognostic scores of 3 to 4 (41%).

Treatment

In total, 315 courses of SMILE were given to 86 patients. A 63-year-old recruited woman died from a fatal stroke before treatment (Table 2). The median number of courses of SMILE administered was 3 (0-6). Eighty-one patients (93%) received >2 courses of SMILE. On confirmation of CR at interim analysis, 19 patients received sandwiched radiotherapy, at a median dose of 50 (30-52) Gy. HSCT was performed in 24 patients after >2 courses of SMILE (allogeneic: 10 patients, all at CR; autologous: 14, with 11 at CR, 2 at PR, and 1 with progressive lymphoma). For the 14 patients undergoing autologous HSCT, harvesting of peripheral blood HSCs was unimpeded by previous SMILE treatment.

Adverse effects of SMILE

Hematologic toxicity developed in every patient (Table 2). Grade 3/4 neutropenia occurred in 67% of cases, despite granulocyte colony-stimulating factor (G-CSF) administration starting on day 7 per protocol. All patients required empirical antimicrobial treatment. Serious infections happened in 27 patients (31%), with 8 patients (9%) requiring admission into intensive care unit, leading to 5 deaths (6%). It should be noted that 4 of the patients dying from sepsis had refractory lymphoma at the time of death. Grade 3/4 thrombocytopenia was also common (42%), although no death resulted. Hepatotoxicity manifesting as increases in transaminases occurred mainly during L-asparaginase treatment. It was reversible, although treatment might be delayed. Five cases had serious liver function derangement. Because they all had advanced diseases, regimen-related toxicity or lymphomatous infiltration could not be clearly differentiated. Nephrotoxicity was mainly attributable to high-dose methotrexate. One patient developed acute renal failure after methotrexate administration during the second course of SMILE. He required hemodialysis, and died from complications. Minor allergic reactions to L-asparaginase happened in about half of the cases. One woman developed angioneurotic edema and anaphylaxis requiring resuscitation. She was switched to Erwinase (EUSA Pharma) without further problems. The frequencies of adverse effects were comparable between newly

Table 1. Demographic and clinicopathologic features of 87 patients with NK/T-cell lymphoma treated with the SMILE regimen

Clinicopathologic parameter	Newly diagnosed	Relapse/ refractory	Overall
No.	43	44	87
Sex			
Male	25	34	59
Female	18	10	28
Median age (range), y	53 (26-83)	49 (23-73)	51 (23-83)
Median time to relapse (range), mo*	NA	6 (1-168)	NA
Primary site (%)†			
Nasal	29	31	60 (69)
Nonnasal	11	10	21 (24)
Disseminated	3	3	6 (7)
Other involved sites (%)‡			
Multiple sites	20	12	32 (37)
Lymph nodes	2	7	9 (10)
Skin	0	4	4 (5)
liver	0	1	1 (1)
Spleen	0	1	1 (1)
Testis	0	1	1 (1)
Gastrointestinal tract	2	2	4 (5)
Raised lactate dehydrogenase§	26	22	48 (55)
Hypoalbuminemia‖	25	26	51 (59)
Histologic involvement			
Bone marrow	14	7	21 (24)
Peripheral blood	1	2	3 (3)
ECOG performance status (%)			
0	26	30	56 (64)
1	11	10	21 (24)
2	6	4	10 (11)
Stage (%)			
I	12	13	25 (29)
II	5	8	13 (15)
III	0	2	2 (2)
IV	26	21	47 (54)
IPI (%)			
Low (0 or 1)	16	18	34 (39)
Intermediate low (2)	7	9	16 (18)
Intermediate high (3)	11	14	25 (29)
High (4 or 5)	9	3	12 (14)
Korean prognostic scoring (%)			
0	10	10	20 (23)
1	7	10	17 (20)
2	4	9	13 (15)
3	8	9	17 (20)
4	14	4	18 (21)

NA indicates not applicable; and ECOG, Eastern Cooperative Oncology Group.

*Either time from diagnosis to refractory disease, or time from last remission to relapse.

†Symptomatic site that was initially biopsied.

‡Involved sites that were asymptomatic or shown up on imaging studies.

§Higher than the upper limit of normal taken in the respective institutes.

‖Lower than the lower limit of normal in the respective institutes.

diagnosed and relapsed/refractory patients (Table 2). Because of adverse effects, 26 patients had dose reduction in methotrexate, ifosfamide, L-asparaginase, or prednisolone during 58 courses of SMILE (Table 2).

Treatment outcome

For the whole cohort, interim analysis showed a CR rate of 56% and a PR rate of 22%, giving an ORR of 78%. On completion of treatment, CR rate was improved to 66%, with the PR rate at 15%, giving an ORR of 81%. The outcome of newly diagnosed and relapsed/refractory patients was presented in Table 3. Interestingly, the interim and completion response rates were comparable for newly diagnosed or relapsed/refractory patients, as well as for lymphomas at different sites of presentation. At a median follow up of 31 months (1-84 months), 47% of patients had remained in remission, with 32% having received SMILE only, and 15% having undergone HSCT while in CR. Thirteen CR patients (15%) had relapsed, all of whom had stage III/IV disease on recruitment. For the 24 cases with PR or nonremission, only 2 patients achieved a remission with salvage treatment.

Prognostic indicators for CR

For the entire cohort, univariate analysis showed that age, albumin, performance score, IPI, and Korean prognostic scores significantly impacted on CR rates (Table 4). Age, performance status, and IPI were significant predictors for CR in newly diagnosed patients; sex

Table 2. Major adverse effects of SMILE in 87 patients with NK/T-cell lymphoma

	No. of patients (%)	All cases	Newly diagnosed	Relapsed/ refractory	*P*
No. of SMILE cycles					
0	1 (1)				
1	5 (6)				
2	21 (24)				
3	21 (24)				
4	13 (15)				
5	3 (3)				
6	23 (26)				
Adverse effect*					
Neutropenia					
Grade 1-2		28 (33)	16	12	
Grade 3/4		58 (67)	26	32	.28
Thrombocytopenia					
Grade 1/2		50 (58)	27	23	
Grade 3/4		36 (42)	15	21	.26
Hepatotoxicity					
Grade 1/2		52 (60)	29	23	
Grade 3/4		6 (7)	5	1	.19
Nephrotoxicity					
Grade 1/2		14 (16)	8	6	
Grade 3/4		1 (1)	1	0	.40
Allergy					
Grade 1/2		43 (49)	16	27	
Grade 3/4		1 (1)	1	0	.20
Dose reduction					
Methotrexate					
1 cycle		3 (3)			
2 cycles		3 (3)			
3 cycles		5 (6)			
4 cycles		4 (5)			
Ifosfamide†					
1 cycle		3 (3)			
3 cycles		2 (2)			
L-Asparaginase					
1 cycle		7 (8)			
2 cycles		1 (1)			
3 cycles[2]		3 (3)			
Prednisolone‡					
2 cycles		1 (1)			

*According to the most serious grade of all cycles.

†Dose reduction of both methotrexate and ifosfamide in 1 patient, and methotrexate, L-asparaginase, and ifosfamide in 2 patients.

‡Omitted because of steroid-induced psychosis. She also had methotrexate dose reduction.

Table 3. Outcome of 87 patients with NK/T-cell lymphoma treated with SMILE

Treatment and outcome	Nasal	Nonnasal	Disseminated	Overall
Newly diagnosed patients				
No. of patients	29	11	3	43
Median total courses of SMILE (range)	4 (0-6)	3 (2-6)	2 (1-3)	4 (0-6)
Regimen-related toxic death	2 (7)	1 (9)	0	3 (7)
Outcome on interim analysis*				
CR	20 (69)	4 (36)	2 (67)	26 (60)
PR	5 (17)	3 (27)	1 (33)	9 (21)
Nonremission	2 (7)	3 (27)	0	5 (11)
Outcome on completion of treatment†				
CR	20 (69)	6 (55)	2 (67)	28 (65)
PR	6 (21)	2 (18)	0	8 (19)
Nonremission	1 (3)	2 (18)	1 (33)	4 (9)
Clinical course of patients with complete remission				
Continued remission	15	1	0	16
Continued remission after HSCT	2	2	1	5
Relapse after SMILE or HSCT	2	3	1	6
Death due to unrelated causes while still in remission‡	1	0	0	1
Outcome of patients with PR or nonremission				
Remission after salvage treatment	1	0	0	1
Surviving with disease	1	2	0	3
Death due to progressive disease	5	2	1	8
Relapsed/refractory patients				
No. of patients	31	10	3	44
Median total courses of SMILE (range)	3 (1-6)	3 (1-6)	4 (3-6)	3 (1-6)
Regimen-related toxic death (%)	2 (6)	1 (10)	0	3 (7)
Outcome on interim analysis*				
CR (%)	14 (45)	7 (70)	2 (67)	23 (52)
PR (%)	8 (26)	1 (10)	1 (33)	10 (23)
Nonremission (%)	6 (19)	1 (10)	0	7 (16)
Not performed (%)	1 (3)	0	0	1 (2)
Outcome on completion of treatment†				
CR (%)	20 (65)	7 (70)	2 (67)	29 (66)
PR (%)	3 (10)	1 (10)	1 (33)	5 (11)
Nonremission (%)	6 (19)	1 (10)	0	7 (16)
Clinical course of patients with CR				
Continued remission	10	1	1	12
Continued remission after HSCT	6	1	1	8
Relapse after SMILE or HSCT	3	4	0	7
Death due to subsequent therapy§	1	0	0	1
Death due to unrelated causes‖	0	1	0	1
Outcome of patients with PR or nonremission				
Remission after salvage treatment	1	0	0	1
Surviving with disease	0	1	0	1
Lost to follow-up	1	0	0	1
Death due to progressive disease	7	1	1	9

*After 2 or 3 courses of SMILE.
†On completion of all SMILE therapy.
‡Death due to dermatomyositis.
§Death during autologous HSCT.
‖Death due to substance abuse.

in relapsed/refractory patients; and Korean prognostic scores in both patient groups. Multivariate analysis showed that sex, age, and albumin remained significant independent factors impacting on CR (Table 5).

Survivals

The estimated 5-year OS was 49.9 ± 12.5% for the whole cohort, 47.4 ± 18.4% for newly diagnosed patients, and 52.3 ± 17.2% for relapsed/refractory patients ($P = .96$; Figure 1A). The estimated 4-year DFS was 63.7 ± 16.2% for the whole cohort, 60.0 ± 22.9% for newly diagnosed patients, and 68.2 ± 22.5% for relapsed/refractory patients ($P = .71$; Figure 1B).

Prognostic factors for OS

Univariate analysis showed that significant factors for the whole cohort included bone marrow infiltration ($P = .001$), stage ($P = .001$), IPI ($P < .001$), and Korean prognostic score ($P < .001$). For newly diagnosed patients, bone marrow infiltration ($P < .001$), IPI ($P = .002$), and Korean prognostic score ($P = .002$) were significant factors. For relapsed/refractory patients, Korean prognostic score ($P = .05$) was the only significant factor. Multivariate analysis showed that IPI ($P = .001$) and age ($P = .023$) remained significant independent factors for the whole cohort, whereas bone marrow involvement significantly impacted on OS for newly diagnosed patients (Table 5; Figure 1C-D).

Table 4. Univariate analyses of prognostic factors for remission after SMILE therapy

	Whole cohort (N = 87)						Newly diagnosed patients (N = 43)						Relapsed/refractory patients (N = 44)					
	Interim			Completion			Interim			Completion			Interim			Completion		
Parameter	CR	Non-CR	*P*	CR	Non-CR	*P*	CR	Non-CR	*P*	CR	Non-CR	*P*	CR	Non-CR	*P*	CR	Non-CR	*P*
Mean age, y*	47.3	53.6	.020	47.5	55.0	.008	48.2	57.7	.017	48.9	57.7	.033	46.4	50.3	.397	46.2	52.3	.661
Mean albumin, g/L*	36.7	34.7	.176	36.9	33.7	.036	36.5	31.9	.064	36.6	31.0	.023	36.9	37.0	.790	37.2	36.5	.799
Sex																		
Male	39	20		45	14		18	7		19	6		21	13		26	8	
Female	10	18	.008	12	16	.002	8	10	.068	9	9	.078	2	8	.020	3	7	.006
Bone marrow																		
Not involved	40	26		46	20		22	7		22	7		18	19		24	13	
Involved	9	12	.153	11	10	.146	4	10	.003	6	8	.033	5	2	.269	5	2	.737
PS																		
0	33	23		41	15		19	7		22	4		14	16		19	11	
1	8	13		8	13		2	9		1	10		6	4		7	3	
2	8	2	.072	8	2	.009	5	1	.004	5	1	< .001	3	1	.485	3	1	.856
Stage																		
I	18	7		20	5		11	1		10	2		7	6		10	3	
II	7	6		8	5		4	1		4	1		3	5		4	4	
III	2	0		2	0		0	0		0	0		2	0		2	0	
IV	22	25	.121	27	20	.185	11	15	.010	14	12	.158	11	10	.468	13	8	.426
IPI																		
Low	25	9		28	6		15	1		14	2		10	8		14	4	
Intermediate (L)	9	7		10	6		3	4		4	3		6	3		6	3	
Intermediate (H)	9	16		12	13		4	7		5	5		5	9		7	7	
High	6	6	.037	7	5	.046	4	5	.008	5	4	.114	2	1	.455	2	1	.439
KIPI																		
I	12	8		15	5		9	1		9	1		3	7		6	4	
II	16	1		16	1		6	1		6	1		10	0		10	0	
III	6	7		6	7		3	1		2	2		3	6		4	5	
IV	14	21	.002	18	17	.007	8	14	.011	11	11	.084	6	7	.006	7	6	.050

PS indicates performance score; L, low; H, high; and KIPI, Korean IPI.

**P* values obtained by Student *t* test; all other *P* values were obtained by χ^2 test.

Prognostic factors for DFS

Univariate analysis showed that significant factors for the whole cohort included site of presentation ($P = .015$), bone marrow infiltration ($P = .001$), performance status ($P = .001$), and IPI ($P < .001$). For newly diagnosed patients, site of presentation ($P = .003$), bone marrow infiltration ($P = .008$), stage ($P = .014$), IPI ($P = .010$), and Korean prognostic score ($P = .013$) were significant predictors. For relapsed/refractory patients, performance status ($P < .001$) and IPI ($P = .001$) were significant predictors. Multivariate analysis showed that IPI was the only significant factor for the whole cohort. For newly diagnosed patients, site of presentation, bone marrow infiltration, and age were significant factors, whereas for relapsed/refractory patients performance status was the only significant factor (Table 6; Figure 1E-H).

Discussion

This study is of significance in the management of NK/T-cell lymphoma. It is to date the largest series of NK/T-cell lymphomas treated by a uniform protocol. Our results detail the use of a new regimen SMILE in a large number of patients.

This series showed features characteristic of NK/T-cell lymphomas: males outnumbering females by 2-fold, median age of presentation in the fifth decade, and a typical ratio of nasal (70%) to nonnasal (30%) lymphomas.[2] These features suggested that the series might be considered representative without significant inadvertent bias in recruitment.

We showed that SMILE of up to 6 courses could feasibly be administered to patients of diverse age groups and performance status, with newly diagnosed or relapsed/refractory diseases, and in early to advanced stages. However, the regimen requires care in administration. Neutropenia can be severe, despite routine G-CSF support. 5 deaths were attributable to sepsis, although predominantly in the context of refractory lymphoma. Therefore, early treatment of infections and the timely use of G-CSF are paramount. Methotrexate toxicity is another issue, with one death because of nephrotoxicity. Daily monitoring of methotrexate level and renal function is mandatory, and folinic acid should be administered until methotrexate levels fall below the toxic ranges. L-Asparaginase causes liver function impairment and allergic reactions. Skin test before each dose is recommended, with the option of changing *E coli* L-asparaginase to Erwinase. Other precautions needed to ensure successful administration of SMILE can be found in supplemental Methods.

The ORR of SMILE for the whole cohort was 78% at interim and 80% on completion, showing that it was a highly effective regimen that induced a swift response. Interestingly, the response rates of newly diagnosed patients receiving SMILE as upfront therapy were similar to those of relapsed/refractory patients receiving SMILE as salvage. This is usually not the case with other chemotherapeutic regimens, which are more effective in newly diagnosed than relapsed/refractory patients. In relapsed/refractory malignancies, resistance to chemotherapy is often related to residual tumor expressing P-glycoprotein that confers an MDR phenotype. SMILE is designed purposefully to include drugs unaffected by MDR. Hence, the similar response rates to SMILE

Table 5. Multivariate analysis of prognostic factors for complete remission and survivals after SMILE therapy

Significant factor	*P*	Hazard ratio	95% confidence interval
CR			
Whole cohort			
Interim			
Sex	.011	3.593	1.333-9.687
Age	.027	1.046	1.005-1.088
Completion			
Sex	.008	4.168	1.456-11.918
Age	.011	1.058	1.013-1.105
Albumin	.023	0.913	0.844-0.987
Newly diagnosed			
Interim			
KIPI	.007	2.654	1.304-5.401
Completion			
Albumin	.017	0.884	0.800-0.978
Age	.023	1.074	1.010-1.143
Relapsed/refractory			
Interim			
Sex	.029	6.667	1.210-36.741
Completion			
Sex	.015	7.000	1.454-33.696
Survivals			
OS			
Whole cohort			
IPI	.001	1.758	1.253-2.466
Age	.023	1.029	1.004-1.055
Newly diagnosed			
Bone marrow involvement	.001	5.186	1.950-13.795
Age	.001	1.073	1.029-1.118
DFS			
Whole cohort			
IPI	.033	1.840	1.049-3.227
Newly diagnosed			
Site	.005	8.490	1.938-37.188
Age	.011	1.162	1.035-1.303
Bone marrow involvement	.031	6.924	1.188-40.348
Relapsed/refractory			
Performance status	.003	6.086	1.864-19.872

KIPI indicates Korean prognostic score.

for upfront treatment and salvage for relapsed/refractory diseases might represent an indirect validation of this strategy. It is also important to point out that the stage of the lymphoma, both for newly diagnosed and relapsed/refractory patients, had no impact on patient outcome and survival, indicating that the regimen was equally efficacious for early and late-stage NK/T-cell lymphoma.

In newly diagnosed cases, despite a high proportion of poor-risk patients (stage III/IV disease: 60%, IPI of 3 to 5: 46%, Korean prognostic score of 3 to 4: 57%), SMILE still resulted in an interim ORR of 81%. The importance of this finding is several-fold. Primary anthracycline-containing chemotherapy regimens, even for stage I/II disease, resulted in low responses of 40% to 60%.[2,14] Disease progression during conventional chemotherapy occurred in 30% to 40% of patients, necessitating salvage radiotherapy. Finally, 30% to 40% of patients would relapse, so that the failure rate of conventional chemotherapy might reach 70%.[2,14] To overcome this problem, concomitant chemoradiotherapy has been tried. In two phase 2 trials comprising 63 patients with stage I/II nasal NK/T-cell lymphoma,[13,15] first-line concomitant chemoradiotherapy resulted in a mean ORR of 82%. Problems with concomitant chemoradiotherapy included serious mucosal toxicity, severe myelosuppression, and logistic difficulties of expeditious radiotherapy for an aggressive lymphoma. Furthermore, concomitant chemoradiotherapy has only been tested in stage I/II good-risk patients and is obviously not useful in diseases of more advanced stages. We showed that at interim analysis, SMILE without radiotherapy resulted in similar to superior response rates, even in patients with advanced stage and poor-risk diseases, compared with concomitant chemoradiotherapy. Furthermore, SMILE offers the advantages of easier logistics, leading to immediate treatment. There is ample time for planning of sandwiched-radiotherapy, and patients are in much better shape when radiotherapy is given. Because many patients are potentially curable, the side effects of radiotherapy, particularly when the field encroaches on important organs, need to be carefully considered and discussed with the patients.

For relapsed/refractory cases, SMILE induced an interim ORR of 75%, again despite frequent poor risks (stage III/IV disease: 52%, IPI of 3-5: 39%, Korean prognostic score of 3-4: 30%). The results of conventional salvage treatments for relapsed/refractory NK/T-cell lymphomas are scanty, owing chiefly to the very poor outcome of these patients.[2] Even-high dose chemotherapy with autologous HSCT resulted in few responses and practically no long-term survivals in relapsed/refractory patients.[16] Our results are therefore notable in several respects. The high interim response rates mean that transplant-eligible patients can be promptly evaluated for HSCT, with mobilization/harvesting of HSC performed before heavy treatment makes the process difficult. In fact, HSC mobilization in all our cases was successful after 2 or more courses of SMILE therapy. Furthermore, an imperative prerequisite for favorable outcome of HSCT in NK/T-cell lymphoma is remission at the time of transplantation.[16] In this study, 8/29 (28%) of relapsed/refractory patients achieving CR successfully underwent HSCT and had remained in remission. More remarkable, however, was that 12/29 (41%) of relapsed/refractory patients had remained in remission on completion of SMILE treatment. The implication is that after SMILE treatment for relapsed/refractory NK/T-cell lymphoma, HSCT may not always be necessary for consolidation to attain a durable remission. This contention is different from the current strategy for other high-grade lymphoid malignancies in second or more advanced remissions, where HSCT is regarded necessary for long-term remission.

Approximately 20% of patients failed to respond. Although the disease extent as reflected by the Korean prognostic score was important for both newly diagnosed and relapsed/refractory patients, it seemed that for newly diagnosed patients the general physique (older age, poor performance status) was important, whereas intriguingly the female sex predicted a poor outcome in relapsed/refractory patients. With multivariate analysis for the whole cohort, female sex, increasing age and low albumin were independent poor risks.

The 5-year OS for the whole cohort was 50%. Interestingly, the OS did not differ significantly between newly diagnosed and relapsed/refractory disease, consistent with the similar ORR of SMILE in these 2 patient groups. The risk factors negatively impacting on OS were similar for both newly diagnosed and relapsed/refractory patients, being related to the extent of disease. On multivariate analysis, IPI was the most important predictor.

The DFS for the whole cohort was 64%. We elected to use DFS instead of progression-free survival, because a substantial proportion of patients actually achieved CR, and PR patients would progress without stable disease. Again, similar to OS, the DFS did not differ between newly diagnosed and relapsed/refractory disease. For newly diagnosed patients, the site of presentation

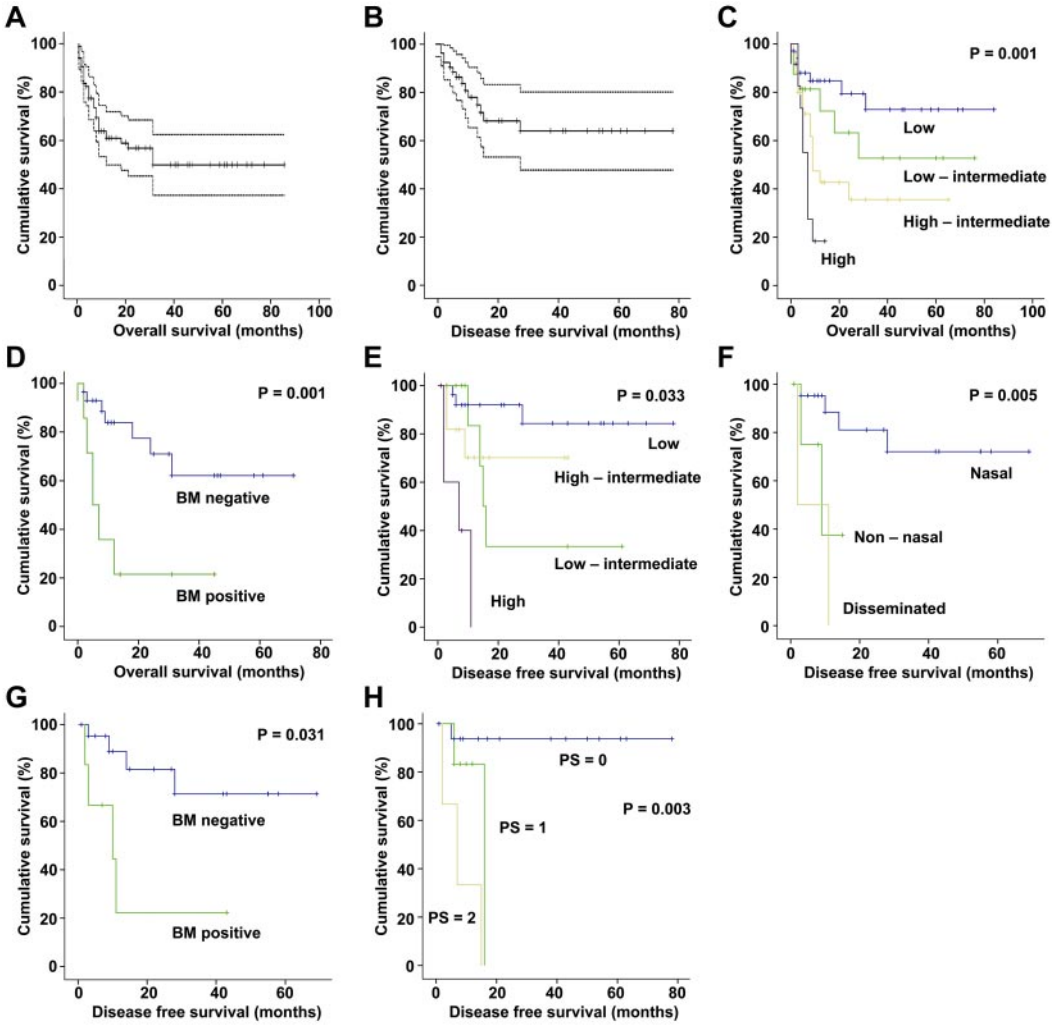

Figure 1. Survivals of patients with NK/T-cell lymphoma treated with the SMILE regimen. (A) OS for the whole cohort. Dotted lines represent 95% confidence intervals. (B) DFS for the whole cohort. Dotted lines represent 95% confidence intervals. (C) Significant impact of IPI on OS. (D) Significant impact of bone marrow (BM) infiltration on OS for newly diagnosed patients. (E) Significant impact of IPI on DFS. (F) Significant impact of initial site of presentation on DFS for newly diagnosed patients. (G) Significant impact of BM infiltration on DFS for newly diagnosed patients. (H) Significant impact of performance status (PS) on DFS for relapsed/refractory patients.

significantly impacted on DFS, whereas the performance status was significant for relapsed/refractory patients. On multivariate analysis, IPI was again the only significant predictor.

These survival analyses showed that the IPI was the most important prognostic factor. Originally devised for aggressive B-cell lymphoma,[17] the IPI has previously been shown to be significant in nasal NK/T-cell lymphoma treated with conventional chemotherapy and radiotherapy.[14] Interestingly, in this study of a new regimen SMILE, IPI was still the most important prognostic indicator for NK/T-cell lymphoma. The Korean prognostic score, devised for NK/T-cell lymphoma treated with conventional anthracycline-containing regimens[18] was not an independent prognostic factor when SMILE was used.

It would be useful to compare our results with those previously described for NK/T-cell lymphomas. In two phase 2 trials comprising 63 patients with good-risk stage I/II nasal NK/T-cell lymphoma,[13,15] first-line concomitant chemo-radiotherapy resulted in a mean ORR of 82% (mean CR, 78%; mean PR, 4%). Seventeen patients in this study had newly diagnosed stage I/II disease. Their interim CR rate before radiotherapy was 88% (Table 4), showing that SMILE chemotherapy alone without radiotherapy achieved results comparable with concomitant chemo-radiotherapy. As for relapsed/refractory lymphoma, an L-asparaginase containing regimen AspaMetDex was reported previously.[19] Response was only evaluated in a relatively small number of 18 patients, with a CR rate of 61%. Because the study was conducted in 13 centers, with most centers only therefore reporting 1 patient, significant selection bias would have existed. Furthermore, risk categorization was not given in that study. In our study, the overall CR rate of 44 relapsed/refractory patients was 66%. As shown in Table 4, for low-risk relapse/refractory patients, the CR rate was actually 80%, compared with 50% in high-risk patients, highlighting that risk categorization must be considered in interpreting treatment outcome.

A limitation in this study was a difference in recruitment in the participating centers. In the center that recruited the largest number of patients, consecutive patients were recruited. However, in 2 other centers, patients with stage I/II disease were not recruited, with only poor-risk patients (stage III/IV, relapsed/refractory disease) included. Therefore, there might have been a bias toward selecting patients with poor risks, which could have negatively affected the overall outcome. Circulating EBV DNA levels have been observed to be important in prognostication in NK/T-cell lymphoma.[20] However, because the assay method of EBV DNA

differed in participating centers, results of this test have not been evaluated.

The results in this study represent an important milestone. This is the first time that a regimen has been shown to have a response rate of as high as 80% for NK/T-cell lymphoma patients across all categories of age, disease status, stages, and IPI scores. Our data establish SMILE as a current standard regimen for NK/T-cell lymphoma. The regimen has toxicity, but with careful attention to adverse effects and skill acquired through experience, it can be safely administered.

Our findings have important implications on future treatment strategies. Female patients of advanced age with low serum albumin have the worst prognosis for remission. Alternative strategies may be needed for these patients. High IPI portended poor OS and DFS, but they did not independently affect CR, suggesting that the adverse impact was mediated through increases in relapses. Hence, for patients with high IPI achieving a remission with SMILE, additional treatment will be needed to prevent relapses. Prospective studies are needed to determine whether HSCT in remission may be beneficial for these patients. Patients not reaching a remission after SMILE have dismal outcome and should be considered candidates for clinical trials of novel agents.

Authorship

Contribution: Y.-L.K., W.S.K., S.T.L., S.J.K., T.T., E.T., A.Y.H.L., and C.-S.C. treated the patients, analyzed the data, and wrote and approved the manuscript.

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