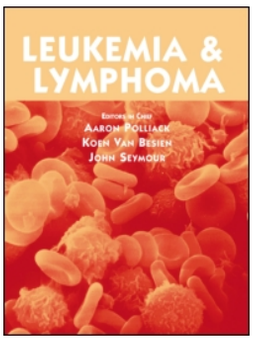

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Encouraging experience in the treatment of nasal type extra-nodal NK/T-cell lymphoma in a non-Asian population

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ABSTRACT

Extra-nodal NK/T-cell lymphoma, nasal type (EN-NK/TCL-NT), is rare in the Western world. We launched the current single-institutional retrospective study with Institutional Review Board approval to better understand the disease. 43 EN-NK/TCL-NT patients treated from 1996 to 2014 were analyzed, including 10 (23%) Asians and 33 (76%) non-Asians. 19/26 (73%) early-stage patients received short-course chemotherapy followed by radiotherapy. 14/17 (82%) advanced-stage patients received primary chemotherapy. Complete response rate was significantly higher in the modified-SMILE group than the accelerated-CHOP group (80% vs. 30%, $p = 0.015$). The 2-year overall survival (OS) and progression-free survival (PFS) were 60% and 40%, respectively. Early-stage disease had significantly higher 2-year OS (87% vs. 21%) and PFS (56% vs.18%) than advanced-stage ($p < 0.001$). Ethnicity had no prognostic difference. EN-NK/TCL-NT in non-Asians shared similar disease characteristics and treatment outcomes with Asians. Most early-stage patients have achieved durable remissions. Management of advanced-stage disease remains challenging, with frequent progression and high mortality.

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Drug therapy; ethnology; extranodal NK-T-cell lymphomas; radiotherapy; SMILE

Introduction

Extranodal NK/T-cell lymphoma, nasal type (EN-NK/TCL-NT) is a rare disease, initially recognized as a distinct entity in The World Health Organization classification in 2001.[1] It is predominantly an extranodal lymphoma with the nasal cavity the most common but non-exclusively involved site. EN-NK/TCL-NT has more commonly been observed in Asian populations.[2] Notably, data from the SEER registry database report an increase in the incidence of EN-NK/TCL-NT in the U.S. from 1992 to 2005.[3]

Historically, EN-NK/TCL-NT was considered an aggressive disease with poor treatment outcomes.[2,4] Reports showed resistance of tumor cells to anthracycline-containing combination chemotherapy, with 5-year survival rates of less than 30%, which questioned the benefit of extensive chemotherapy.[2,5] Since the last decade, many retrospective analyzes and several prospective clinical trials from the Far East have been published. By emphasizing radiotherapy (RT) as the primary treatment [5–9] and with the introduction of evolving new anti-multidrug resistance (MDR) regimens,[6,7,10–12] a better understanding of the nature of the disease and improved outcomes for localized disease have become possible.

There is currently limited data on Caucasian populations, yet the few published series demonstrated extremely poor prognosis.[11,13] The underlying reasons for the diverse prognosis of these patients compared to those from recent Asian studies remain unclear, as baseline characteristics have many similarities.

Therefore, we launched a retrospective study at our center to gain a better understanding in a U.S. center of the disease's current presentation and treatment outcome.

Materials and methods

Study population

After obtaining institutional review board (IRB) approval, we retrospectively collected data of EN-NK/TCL-NT patients consecutively diagnosed and treated at our center from January 1996 to December 2014. In

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total, 62 cases were pathologically confirmed as EN-NK/TCL-NT. Fourteen patients were identified as having no treatment at our center, were quickly lost to follow-up after diagnosis and were excluded from the analysis. Five patients with previous undocumented or unclear treatment outside our center prior to diagnosis were also excluded from the analysis. All 43 patients treated at our center were included in the study. Patients underwent standard staging procedures with routine physical and endoscopic examination; biochemistry; computed tomography and/or magnetic resonance imaging of the head and neck, chest, abdomen and pelvis; and a bone marrow examination. Positron emission tomography (PET) was routinely employed in staging and response evaluation after 2002. Random biopsies were not performed for apparently normal areas during endoscopic examination. Basic patient characteristics, treatment responses and outcomes were reviewed through patient medical records.

Treatment strategy

According to institutional guidelines, patients with early stage disease were treated with short-course chemotherapy and involved site radiation therapy (ISRT); patients with advanced stage disease were treated with intensive chemotherapy, often followed by consolidated bone marrow transplantation in responders. The treated volume encompasses the primary evident macroscopic tumor at presentation (pre-chemotherapy if upfront chemotherapy was delivered) with an expansion of 2 cm accounting for the potential sites of microscopic disease. Prior to 2009, accelerated-CHOP (acc-CHOP) or CHOP-like regimens were employed at our center; after 2009, a modified SMILE (m-SMILE) regimen was prospectively introduced and has become the preferred regimen. The drug doses and the administration schedule of m-SMILE were as follows: methotrexate, 2000 mg/m^2 intravenously on day 1; dexamethasone, 40 mg/day intravenously on days 2–4; ifosfamide, 1500 mg/m^2 intravenously on days 2–4; etoposide, 100 mg/m^2 on days 2–4; and Pegasparaginase 1500–2500 IU/m^2 intravenously or intramuscularly on day 8. This regimen was repeated every 21 days.

Radiotherapy of 45 Gy was given in fractions of 1.8 Gy five times weekly to the involved site with a safety margin of 1–2 cm; prophylactic regional node irradiation was not administered.

Response criteria

Treatment responses were assessed using standard criteria.[14] A complete response (CR) was defined as no evidence of residual disease including FDG negativity in subjects who underwent PET imaging; a partial response (PR) as at least a 50% reduction in tumor burden compared to the beginning of treatment; stable disease (SD) as failure to attain the criteria needed for a CR or PR, but does not fulfill those for progressive disease; and relapsed disease (after CR)/progressive disease (PD) (after PR or SD) as the appearance of any new lesion or at least a 50% increase in lesion size. Responses were assessed from clinical, radiological and laboratory studies three months after treatments.

Endpoints and statistical evaluation

Overall survival (OS) was calculated from the date of diagnosis to the date of death or date of the last follow-up. Progression free survival (PFS) was measured from the date of diagnosis to the date of tumor progression/recurrence or death from any cause. When no event occurred, the patient was censored at the last date of follow-up.

The characteristics of the patients were compared by race with the use of the Fisher's exact test for categorical variables. Time-to-event endpoints were estimated using the Kaplan–Meier method, and compared between groups using log-rank tests. Within subgroups where the number of events is few, comparisons were assessed by permuted log rank test.[15]

Role of the funding source

The sources of funding had no involvement in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Results

Patients characteristics

The characteristics of 43 patients are listed in Table 1. Among them, 10 (23%) were Asian, 32 (74%) were Caucasian and one was African American. The median age was 53 years (range 24–81). The patient cohort was male predominant (56%). Twenty-eight patients (65%) presented with upper aerodigestive tract (UADT) lesions, including the nasal cavity in 23 patients and Waldeyer's ring in five patients. Fourteen patients presented with primary extranodal sites other than the head and neck area (non-UADT), including skin (8 patients), lung (3 patients), small bowel (2 patients) and testis (1 patient). For the 23 nasal cavity cases, all but one had paranasal sinus involvement, while

Table 1. Distribution of characteristics in entire cohort and by race.

		Ethnicity		
Characteristic	Entire cohort ($N = 43$)	Asian ($N = 10$)	Non-Asian ($N = 33$)	p value*
Median age at diagnosis (range)	3 (24–81)	56 (29–65)	52 (24–81)	0.78
Gender				0.08
Male	24 (56%)	3 (30%)	21 (64%)	
Female	19 (44%)	7 (70%)	12 (36%)	
Stage				0.99
I, II	26 (61%)	6 (60%)	20 (61%)	
III, IV	17 (39%)	4 (40%)	13 (39%)	
B-symptoms at diagnosis				0.99
Not present/NA	37 (86%)	9 (90%)	28 (85%)	
Present	6 (14%)	1 (10%)	5 (15%)	
Bone marrow biopsy				0.99
Negative	35 (93%)	9 (90%)	26 (79%)	
Positive	3 (7%)	1 (10%)	2 (6%)	
Primary site				0.28
UADT	28 (65%)	5 (50%)	23 (70%)	
Other	15 (35%)	5 (50%)	10 (30%)	
IPI score				0.72
0 or 1 risk score	28 (65%)	6 (60%)	22 (67%)	
2 or higher	15 (35%)	4 (40%)	11 (33%)	
Elevated LDH				0.17
Normal	22 (69%)	3 (30%)	19 (58%)	
Elevated	10 (31%)	4 (40%)	6 (18%)	
ECOG PS				0.61
PS 0 or 1	37 (86%)	8 (80%)	29 (88%)	
PS 2 or higher	6 (14%)	2 (20%)	4 (12%)	

*p value from Wilcoxon's rank sum test or Fisher's exact test. Abbreviations: NA: No information available; UADT: upper aero-digestive tract; IPI: International Prognostic Index; LDH: lactate dehydrogenase; ECOG: Eastern Cooperative Oncology Group; PS: performance status.

5 (22%) patients had cervical node involvement. In total, there were 24 stage I patients, 17 stage IV patients and 2 stage II patients. Notably, 21 of the 28 UADT origin patients were classified as early stage, compared to only 5 of 15 non-UADT early stage patients. When risk factors were assessed, most patients (65%) were in a low-risk International Prognostic Index (IPI) group (IPI 0–1).

Basic characteristics were similar in Asian and non-Asian patients (Table 1).

First-line treatment

Treatment strategies differed profoundly according to stage; Table 2 lists detailed treatment information of the entire cohort.

Treatment in early stage

Among 26 early stage patients, 20 received combined modality treatment (CMT), including 19 with inductive chemotherapy and definitive radiotherapy and one with primary radiotherapy and adjuvant chemotherapy. Two stage I cases received localized irradiation to the involved skin site (RT alone). Four cases received chemotherapy alone.

Of the 20 CMT cases, 14 (70%) received 2–3 cycles of chemotherapy (median cycle number, 2; range, 2–6) and 6 (30%) received 4–6 cycles. Chemotherapy regimens included m-SMILE in 11 cases, acc-CHOP in 6 cases and other in 3 cases. Seventeen (85%) patients received 45 Gy ISRT. The median interval from diagnosis to initiation of RT was 3.6 months; 17 cases (85%) began RT within 6 months.

All chemotherapy alone patients received six cycles of acc-CHOP – 3/4 patients had disease progression during chemotherapy and 1/4 cases had a relapse of three months after chemotherapy.

Treatment in advanced stage

Three patients received no treatment after diagnosis due to their substantially diminished physical condition. The remaining 14 patients received chemotherapy alone (10 cases) or chemotherapy combined with radiation (4 cases). Seven patients also received stem cell transplantation (SCT) after chemotherapy or CMT. Nine patients received m-SMILE and three received acc-CHOP. The majority (11/14, 79%) received less than four cycles of chemotherapy.

Treatment outcome

Response to chemotherapy

Chemotherapy response was evaluated for 37 patients; PET/CT was applied in 27 (73%) cases. We assessed treatment response at two time points: early response

Table 2. Clinical data and primary treatment of 43 accrued patients.

No.	Stage	Race	Primary location	IPI	Treatment	CT	RT	BMT	Progression	Status at last F/U	OS (months)
1	I	White	NC	0	CT + RT	SMILE ×2	ISRT 45Gy	No	No	NED	41.7
2	I	White	NC	0	CT + RT	SMILE ×2	ISRT45Gy	No	No	NED	33.5
3	I	White	WR	0	CT + RT	SMILE ×2	ISRT45Gy	No	No	NED	27.5
4	I	White	NC	1	CT + RT	SMILE ×2	ISRT45Gy	No	No	NED	2.9
5	I	White	NC	1	CT + RT	acc-CHOP ×4	ISRT45Gy	No	No	DOC	86.5
6	I	White	skin	1	CT + RT	acc-CHOP ×3	ISRT30.6Gy	No	No	DOC	186.4
7	I	White	NC	0	CT + RT	ProMACE + CytaBOM ×4	ISRT 30.6Gy	No	Relapse at larynx	DOC	97.2
8	I	White	WR	0	CT + RT	VACOP-V × 6	ISRT45Gy	No	No	NED	137.4
9	I	White	NC	0	CT + RT	acc-CHOP ×6	ISRT45Gy	No	No	NED	77.8
10	I	White	NC	0	CT + RT	SMILE ×3	ISRT45Gy	No	No	NED	6.8
11	I	White	WR	1	CT + RT	SMILE ×2	ISRT45Gy	No	Relapse at NC	NED	31.7
12	I	White	WR	1	CT + RT	SMILE ×2	ISRT45Gy	No	No	NED	18.6
13	I	White	NC	0	CT + RT	SMILE ×2	ISRT45Gy	No	No	NED	13.7
14	I	White	NC	0	CT + RT	SMILE ×2	ISRT45Gy	No	No	NED	5.3
15	I	White	testis	0	CT	acc-CHOP ×6	No	No	Progress during CT	DOD	12.9
16	I	White	NC	0	CT	acc-CHOP ×6	No	No	Progress during CT	DOD	142.1
17	I	White	NC	0	CT	acc-CHOP ×6	No	No	Progress during CT	DOD	10.1
18	I	White	skin	0	RT	–	ISRT50Gy	No	Relapse at bowel and skin	NED	80.5
19	I	White	skin	1	RT	–	ISRT45Gy	No	Relapse at skin	NED	106.8
20	I	Asian	NC	2	CT + RT	SMILE ×2	ISRT45Gy	No	No	NED	35.0
21	I	Asian	NC	1	CT + RT	acc-CHOP ×6	ISRT45Gy	No	No	NED	29.2
22	I	Asian	NC	0	CT + RT	acc-CHOP ×4	ISRT45Gy	No	Relapse at NC and skin	DOD	50.7
23	I	Asian	NC	0	CT + RT	IMEP ×3	ISRT45Gy	No	No	NED	19.8
24	I	Asian	NC	1	RT + CT	acc-CHOP ×2	ISRT45Gy	No	Relapse at larynx	NED	63.9
25	II	White	NC	0	CT + RT	SMILE ×3	ISRT54Gy	Yes	No	NED	45.0
26	II	Asian	small bowel	0	CT	acc-CHOP ×4	No	No	Relapse at lung and LNs	DOD	19.4
27	IV	White	NC	1	CT + RT	SMILE ×3	ISRT36Gy + TBI	Yes	No	DOC	7.2
28	IV	White	NC	2	CT + RT	SMILE ×3	ISRT45Gy + TBI	Yes	No	NED	52.7
29	IV	White	NC	2	CT + RT + CT	SMILE ×3	ISRT36Gy	No	Relapse at skin, lung	DOD	12.2
30	IV	White	small bowel	3	CT	CTX + Etoposide ×2	No	No	Progress during CT	DOD	5.3
31	IV	White	NC	4	CT	SMILE ×3	No	Yes	No	DOC	7.4
32	IV	White	WR	2	CT	VACOP-B × 6	No	No	Relapse at orbit	DOD	10.5
33	IV	White	lung	3	CT	acc-CHOP ×4	No	Yes	No	NED	133.8
34	IV	White	NC	4	CT	acc-CHOP ×1	No	No	Progress during CT	DOD	2.3
35	IV	White	NC	3	CT	acc-CHOP ×1	No	No	Progress during CT	DOD	2.4
36	IV	White	lung	3	others	No treatment	No	No	No treatment	DOD	0.6
37	IV	White	skin	3	others	No treatment	No	No	No treatment	DOD	1.5
38	IV	White	skin	3	others	No treatment	No	No	No treatment	uncertain	4.3
39	IV	Black	LNs	1	CT	SMILE ×2	No	No	Relapse at LN	DOD	5.9
40	IV	Asian	skin	2	CT + RT	SMILE ×2	ISRT54Gy	No	Progress during RT	DOD	10.1
41	IV	Asian	skin	1	CT	SMILE ×3	No	Yes	No	NED	9.6
42	IV	Asian	lung	4	CT	SMILE ×2	No	No	Relapse at CNS	DOD	7.6
43	IV	Asian	NC	4	CT	SMILE ×6	No	Yes	Relapse at skin	AWD	13.2

Abbreviations: NC: nasal cavity; WR: Waldeyer's Ring; LN: lymph node; IPI: International Prognostic Index; OS: overall; CT: chemotherapy; BMT: bone marrow transplantation; RT: radiotherapy; ISRT: involved site radiotherapy; F/U: follow up; DOD: die of disease; NED: no evidence of disease; DOC: die of complications: accidence or other unrelated disease.

after 1–3 cycles for all cases, and late response after 4–6 cycles for those who received long-course chemotherapy.

At early response, CR was recorded in 19 patients (51%), PR in 11 patients (30%), SD in 1 patient (3%) and PD in 3 patients (8%), with no information in 3 patients. CR rate was significantly higher with m-SMILE compared to acc-CHOP (80% [16/20] vs. 30% [3/10], $p = 0.015$), while overall response rate (ORR = CR + PR) was not significantly different (95% [19/20] vs. 80% [8/10], $p = 0.25$). There was no significant difference for CR rate between early stage and advanced stage patients (65% [13/20] vs. 43% [6/14], $p = 0.30$).

Twelve of these 37 patients received 4–6 cycles of chemotherapy (long-course chemotherapy) and late response was assessed after completion of all chemotherapy. With additional chemotherapy (>3 cycles), two PR patients converted to CR, while three PR patients had disease progression.

By the end of chemotherapy (1–6 cycles), CR was recorded in 23 patients (62%), PR in five patients (14%), SD in two patients (5%) and PD in six patients (16%), with one patient not evaluable.

Tumor control with radiotherapy

In total, 26 patients received primary ISRT and four patients received salvage localized irradiation; Twenty-one (70%) cases received Intensity Modulation Radiated Therapy (IMRT)/3-dimensional conformal radiotherapy (3D-CRT). With a median follow-up of 28 months (range, 1–179) from the end of radiation among these 30 cases, only two (7%) developed in-field failures and another three (10%) had disease failure at adjacent sites (one

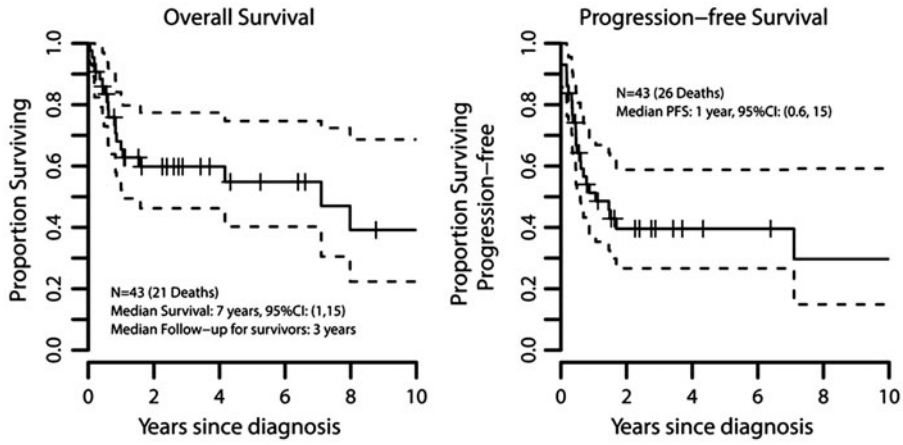

Figure 1. Overall survival and progression-free survival for this cohort. (Magnification 1×).

with disease in the nasopharynx, failed in the nasal cavity; two with disease in the nasal cavity, failed in the larynx).

Outcome for transplantation

SCT was administered in 14 patients, including five with allogeneic and 9 with autologous SCT. Transplantation was employed in six patients as consolidative treatment after initial CR, one patient after initial PR and seven patients as part of salvage treatment after relapse. Two consolidated transplantation patients died of treatment-related complications (one allogeneic and one autologous SCT). Four salvage transplantation patients died of relapsed disease. Overall 6/14 subjects who underwent transplantation are alive and in remission: 2/6 who underwent transplantation in CR (1/3 allogeneic, 1/3 autologous), 1/6 who underwent transplantation after PR (autologous) and 3/7 who underwent transplantation after relapse (all autologous).

Survival

Survival in the total cohort

With a median follow-up among survivors of 2.7 years (range 0.2–11 years), we observed 22 with disease progressions and 21 deaths of any cause. The 2-year OS was 60% (95% CI, 46–77%) and 2-year PFS was 40% (95% CI, 27–59%), as shown in Figure 1.

In three cases, disease progressed rapidly and the patients died before treatment could be initiated. There were six progressions recorded during chemotherapy, one during radiotherapy and 12 after treatment. Treatment failures were defined as local in three cases, distant in eight cases and both in 11 cases. Among the 21 patients who died, 16 died of disease, two died of treatment related complications and three died of other cancers (uterine cancer, cholangiocarcinoma and melanoma). Most deaths occurred within the first 2 years after diagnosis.

The 2-year OS and PFS in early stage were 87% (95% CI, 64–95%) and 56% (95% CI, 33–73%), respectively. The 2-year OS and PFS in advanced stage were 21% (95% CI, 5–43%) and 18% (95% CI, 4–38%), respectively. The prognosis of early stage patients was significantly better than that of advanced stage patients (Figure 2), with $p < 0.05$ in both OS and PFS.

Survival in the m-SMILE group

Among patients with early stage disease, 11 received 2–3 cycles of m-SMILE and 45 Gy of ISRT (one received 54Gy ISRT). With a median follow-up from the start of initial therapy of 2 years (range 0.1–3.6 years), all were alive with no evidence of disease. Only one patient (Case 11 in Table 2) progressed 20 months after start of therapy at the adjacent site. The 2-year estimated PFS rate was 83% (95% CI 27–97%). OS and PFS were borderline significantly better with m-SMILE than acc-CHOP (permuted log rank $p = 0.11$ for OS and $p = 0.03$ for PFS) although follow-up was longer with acc-CHOP (median 5 years; range 0.7–15 months). There were nine advanced stage patients who received m-SMILE, with a median follow-up from the start of therapy of 8.5 months (range 4.3–52 months); seven patients progressed and six died. OS at 6 months was 78% (95% CI 36–94%) and PFS at 6 months was 56% (95% CI 20–80%). At 1 year after diagnosis, only three patients were alive and only one remained progression-free. Advanced stage patients who received m-SMILE

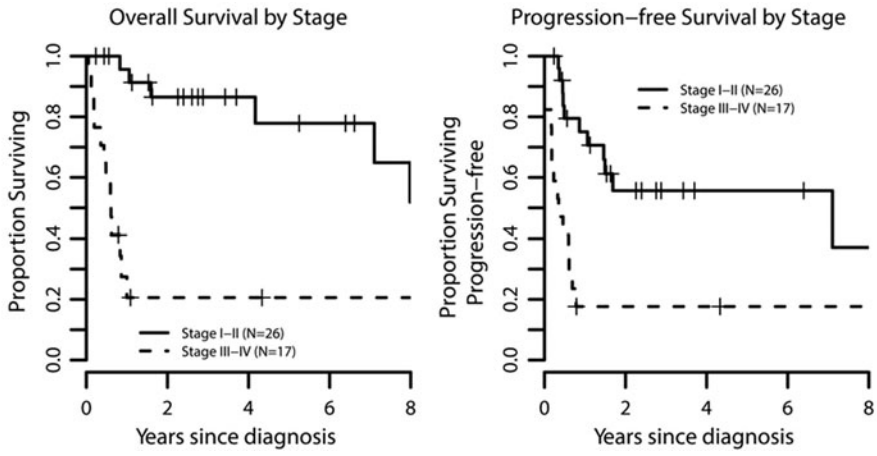

Figure 2. Overall survival and progression-free survival by stage. Early stage patients had a significantly better overall survival and progression free survival than advanced stage patients. (Magnification 1×).

Table 3. Prognostic factors for OS and PFS.

		Overall survival			Progression-free survival		
Characteristic	Total	Number died	2-year OS	Log-rank *p*	Number progressed or died	2-year PFS	Log-rank *p*
Race							
Asian	10	4	66%	0.76	6	35%	0.80
Non-Asian	33	17	58%		20	41%	
Age at diagnosis							
less than 55	25	13	52%	0.48	14	41%	0.90
55 or older	18	8	72%		12	39%	
Gender							
Male	24	11	60%	0.41	13	52%	0.23
Female	19	10	61%		13	22%	
Stage							
I, II	26	8	87%	<0.0001	12	56%	0.0004
III, IV	17	13	21%		14	18%	
B symptoms at diagnosis							
Not present/no information available	37	19	59%	0.74	24	36%	0.34
Present	6	2	63%		2	67%	
Bone marrow biopsy							
Negative	35	15	69%	<0.0001	20	44%	<0.0001
Positive	3	3	0%		3	0%	
Primary site							
UADT	28	11	73%	0.25	13	51%	0.006
Other	15	10	36%		13	18%	
IPI score							
0 or 1 risk score	28	10	79%	0.0006	14	50%	0.005
2 or higher	15	11	27%		12	20%	
Elevated LDH							
Normal	22	8	69%	0.07	12	45%	0.31
Elevated	10	6	34%		6	35%	
ECOG PS							
PS 0 or 1	37	16	67%	<0.0001	20	46%	<0.0001
PS 2 or higher	6	5	17%		6	0%	

Abbreviations: UADT: upper aerodigestive tract; IPI: International Prognostic Index; LDH: lactate dehydrogenase; ECOG: Eastern Cooperative Oncology Group; PS: performance status; OS: overall survival; PFS: progression free survival.

showed similar poor survival compared to patients on acc-CHOP.

Prognostic factors

Early stage, negative bone marrow biopsy, IPI risk score of 0 or 1, and ECOG PS of 0 or 1 were significantly associated with improved OS and PFS. UADT site was significantly associated with improved PFS, but the improvement in OS was not significant (Table 3).

Discussion

Extranodal NK/T-cell lymphoma is rare in the Western world, and there is very little data on Caucasian populations. Our current study provides a single-institution

experience based on a retrospective review of 43 cases (largely Caucasian), and shows a favorable treatment outcome compared to previous Western series.[11,13] With short course chemotherapy followed promptly by ISRT, most early stage patients have achieved durable remissions with a 2-year OS of 87%, with encouraging preliminary results since our incorporation of the m-SMILE regimen with all patients alive and only one progression at the end of follow-up. This promising outcome is attributed to the high response rate of short course chemotherapy with PET/CT evaluation and specifically to excellent local control of radiotherapy with a moderate dose of 45 Gy. The advanced stage patients still remain challenging with few long term survivors using current treatment paradigms. Patients with systemic disease rarely had durable remissions; many progressed during chemotherapy.

The baseline patient and disease characteristics analyzed in the current series show great similarities to those from endemic areas [5–7,12] as well as non-endemic areas.[13,16,17] Similar disease prognostic factors were found between both groups. Patients usually presented in their late 40s and 50s with slight male predominance.[2,4] Disease most often involved the UADT, with occasional regional node dissemination. Although B symptoms occurred less frequently in our series, the overall IPIs were comparable to other reports. We observed similar distributions of baseline characteristics between Caucasian and Asian patients.

In addition to disease characteristics, our current study also confirmed the similarity of Caucasian EN-NK/TCL-NT outcomes to those of Asians, if provided with optimal treatment. In reports from the Far East, when primary radiotherapy with (and sometimes without) anthracycline-based chemotherapy [5] or new anti-multidrug resistant protein (P-glycoprotein) regimen [18,19] was employed as the primary treatment, an overall survival of ~85% by 2 years and 70% by 5 years was recorded in early stage disease. Interestingly, we observed a plateau in the survival curve after 2 years. Most treatment failures and deaths occurred within the first 2 years.

Our current study supports the importance of early radiotherapy for localized disease. Among the 30 patients who received localized RT, only two developed in-field failures. Additionally, RT was an effective salvage treatment for local relapse. When prolonged chemotherapy was administered, three of 11 patients had progressive disease during chemotherapy. Cheung noted that about two-thirds of patients receiving chemotherapy progress during or shortly after CR.[20] Furthermore, Oshimi declared in his paper that response to chemotherapy was transient if administered, and early local relapse and metastasis were common.[21] This information underscores the importance of early RT.

In most Asian studies, a higher RT dose (50 Gy or higher) was involved. Koom defined a sigmoid dose-response curve by observing 102 early stage patients, and thus claimed a higher dose level should be considered when treating these patients with RT alone.[22] Huang reported that a lower RT dose was associated with inferior survival.[23] In our series, ISRT with 45 Gy afforded good local control. However, given the limited numbers of patients in current series, the safety of dose reduction still remains uncertain when effective chemotherapy is applied and when adequate imaging modalities are available for response evaluations.

L-asparaginase was first introduced as part of NK/T-cell lymphoma treatment in 2003 [24] and was found to have high efficacy in inducing apoptosis in vitro in two NK-cell lines.[25] L-asparaginase containing regimens have been studied prospectively in refractory/relapsed disease and advanced disease.[10–12,26] Given the high CR rate (~50%) and overall response rate (around 75–80%) observed in these trials, it was introduced as part of first-line treatment.[18,27] In our cohort, we recorded a very high CR rate and ORR with m-SMILE with PET/CT evaluation. However, as compared to localized disease, in advanced stage disease this higher response rate did not translate to an improvement in overall survival. Kim also reported SMILE and ASCT for stage IV disease.[28] Similarly, though the short term ORR was as high as 59%, the median OS was only 10.6 months due to high treatment-related death rates and disease progression. They also recorded four late relapses among 11 ASCT patients. Their data, together with ours, may suggest that chemotherapy alone, even with SMILE, is insufficient to provide long-term disease remission in most cases. Given the transient response of chemotherapy alone and lack of effective salvage treatment for EN-NK/TCL-NT, we strongly recommend incorporating ISRT as an important element in definitive treatment.

Given the retrospective nature of this study and the limited numbers involved, we are cautious in drawing any definitive conclusions. Many potentially important factors could not be evaluated, such as serum EBV load and its role in prognosis and treatment. However, our non-Asian EN-NK/CL-NT patients were fairly comparable to our Asian patients with respect to basic characteristics and prognosis. We particularly recommend a multi-institutional prospective evaluation of short course m-SMILE or other similarly effective L-asparaginase-containing regimens with prompt ISRT of 45 Gy based on the excellent outcomes among early

stage disease cases recorded in the current study. It is now the recommended treatment at our center to apply two cycles of m-SMILE chemotherapy and 45 Gy ISRT for early stage EN-NK/TCL-NT.

In conclusion, EN-NK/TCL-NT in non-Asians shared similar disease characteristics and treatment outcomes with patients of Asian origin at our institution. Short course m-SMILE chemotherapy induced a high response rate. ISRT of 45 Gy administered immediately following chemotherapy demonstrated excellent local control and was well-tolerated. With short course effective chemotherapy followed promptly by ISRT, most early stage patients have achieved durable remissions. However, advanced stage disease still remains challenging even with current regimens, with frequent progression and high mortality.

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References

[1] Harris NL, Jaffe ES, Diebold J, et al. The world health organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues. Report of the clinical advisory committee meeting, Airlie house, Virginia, november, 1997. Ann Oncol. 1999;10:1419–1432.

[2] Vose J, Armitage J, Weisenburger D, International TCLP. International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. J Clin Oncol. 2008;26:4124–4130.

[3] Abouyabis AN, Shenoy PJ, Lechowicz MJ, et al. Incidence and outcomes of the peripheral T-cell lymphoma subtypes in the United States. Leuk Lymphoma. 2008;49:2099–2107.

[4] Au WY, Weisenburger DD, Intragumtornchai T, et al. Clinical differences between nasal and extranasal natural killer/T-cell lymphoma: a study of 136 cases from the international peripheral T-Cell lymphoma project. Blood. 2009;113:3931–3937.

[5] Li YX, Yao B, Jin J, et al. Radiotherapy as primary treatment for stage IE and IIE nasal natural killer/T-cell lymphoma. J Clin Oncol. 2006;24:181–189.

[6] Kim SJ, Kim K, Kim BS, et al. Phase II trial of concurrent radiation and weekly cisplatin followed by VIPD chemotherapy in newly diagnosed, stage IE to IIE, nasal, extranodal NK/T-Cell lymphoma: consortium for improving survival of lymphoma study. J Clin Oncol. 2009;27:6027–6032.

[7] Yamaguchi M, Tobinai K, Oguchi M, et al. Phase I/II study of concurrent chemoradiotherapy for localized nasal natural killer/T-cell lymphoma: Japan clinical oncology group study JCOG0211. J Clin Oncol. 2009;27:5594–5600.

[8] Wang ZY, Li YX, Wang WH, et al. Primary radiotherapy showed favorable outcome in treating extranodal nasal-type NK/T-cell lymphoma in children and adolescents. Blood. 2009;114:4771–4776.

[9] Yang Y, Zhu Y, Cao JZ, et al. Risk-adapted therapy for early-stage extranodal nasal-type NK/T-cell lymphoma: analysis from a multicenter study. Blood. 2015;126:1424–1432.

[10] Yamaguchi M, Suzuki R, Kwong YL, et al. Phase I study of dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide (SMILE) chemotherapy for advanced-stage, relapsed or refractory extranodal natural killer (NK)/T-cell lymphoma and leukemia. Cancer Sci. 2008;99:1016–1020.

[11] Jaccard A, Gachard N, Marin B, et al. Efficacy of L-asparaginase with methotrexate and dexamethasone (AspaMetDex regimen) in patients with refractory or relapsing extranodal NK/T-cell lymphoma, a phase 2 study. Blood. 2011;117:1834–1839.

[12] Yamaguchi M, Kwong YL, Kim WS, et al. 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. J Clin Oncol. 2011;29:4410–4416.

[13] Pagano L, Gallamini A, Trape G, et al. NK/T-cell lymphomas 'nasal type': an Italian multicentric retrospective survey. Ann Oncol. 2006;17:794–800.

[14] Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007;25:579–586.

[15] Heller G, Venkatraman ES. Resampling procedures to compare two survival distributions in the presence of right-censored data. Biometrics. 1996;52:1204–1213.

[16] Jaccard A, Petit B, Girault S, et al. L-asparaginase-based treatment of 15 western patients with extranodal NK/T-cell lymphoma and leukemia and a review of the literature. Ann Oncol. 2009;20:110–116.

[17] Li S, Feng X, Li T, et al. Extranodal NK/T-cell lymphoma, nasal type: a report of 73 cases at MD Anderson Cancer Center. Am J Surg Pathol. 2013;37:14–23.

[18] Jiang M, Zhang H, Jiang Y, et al. Phase 2 trial of "atural killer/T-cell lymphoma" L-asparaginase, vincristine, and prednisone chemotherapy with radiotherapy in newly diagnosed, stage IE to IIE, nasal type, extranodal natural killer/T-cell. Cancer. 2012;118:3294–3301.

[19] Wang L, Wang ZH, Chen XQ, et al. First-line combination of gemcitabine, oxaliplatin, and L-asparaginase (GELOX) followed by involved-field radiation therapy

for patients with stage IE/IIE extranodal natural killer/T-cell lymphoma. Cancer. 2013;119:348–355.

[20] Cheung MM, Chan JK, Lau WH, et al. Early stage nasal NK/T-cell lymphoma: clinical outcome, prognostic factors, and the effect of treatment modality. Int J Radiat Oncol Biol Phys. 2002;54:182–190.

[21] Oshimi K. Progress in understanding and managing natural killer-cell malignancies. Br J Haematol. 2007;139:532–544.

[22] Koom WS, Chung EJ, Yang WI, et al. Angiocentric T-cell and NK/T-cell lymphomas: radiotherapeutic viewpoints. Int J Radiat Oncol Biol Phys. 2004;59:1127–1137.

[23] Huang MJ, Jiang Y, Liu WP, et al. Early or up-front radiotherapy improved survival of localized extranodal NK/T-cell lymphoma, nasal-type in the upper aerodigestive tract. Int J Radiat Oncol Biol Phys. 2008;70:166–174.

[24] Yong W, Zheng W, Zhang Y, et al. L-asparaginase-based regimen in the treatment of refractory midline nasal/nasal-type T/NK-cell lymphoma. Int J Hematol. 2003;78:163–167.

[25] Ando M, Sugimoto K, Kitoh T, et al. Selective apoptosis of natural killer-cell tumours by l-asparaginase. Br J Haematol. 2005;130:860–868.

[26] Kwong YL, Kim WS, Lim ST, et al. SMILE for natural killer/T-cell lymphoma: analysis of safety and efficacy from the Asia lymphoma study group. Blood. 2012;120:2973–2980.

[27] Zhou Z, Li X, Chen C, et al. Effectiveness of gemcitabine, pegaspargase, cisplatin, and dexamethasone (DDGP) combination chemotherapy in the treatment of relapsed/refractory extranodal NK/T cell lymphoma: a retrospective study of 17 patients. Ann Hematol. 2014;93:1889–1894.

[28] Kim SJ, Park S, Kang ES, et al. Induction treatment with SMILE and consolidation with autologous stem cell transplantation for newly diagnosed stage IV extranodal natural killer/T-cell lymphoma patients. Ann Hematol. 2015;94:71–78.