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ORIGINAL ARTICLE

Sequential chemotherapy/radiotherapy was comparable with concurrent chemoradiotherapy for stage I/II NK/T-cell lymphoma

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Background: In stage I/II natural killer (NK)/T-cell lymphoma, concurrent chemoradiotherapy (CCRT) had previously been shown to result in superior outcome compared with anthracycline-containing regimens, which have since been considered ineffective. The role of CCRT in comparison with approaches employing nonanthracycline-containing chemotherapy (CT) and sequential radiotherapy (RT) in such patients remains to be defined.

Patients and methods: Three hundred and three untreated patients (207 men, 96 women; median age: 51, 18–86 years) with stage I/II NK/T-cell lymphoma who had received nonanthracycline-containing regimens were collected from an international consortium and retrospectively analyzed. Treatment included single modality (CT and RT), sequential modalities (CT + RT; RT + CT) and concurrent modalities (CCRT; CCRT + CT). The impact of clinicopathologic parameters and types of treatment on complete response (CR) rate, progression-free-survival (PFS) and overall-survival (OS) was evaluated.

Results: For CR, stage ($P = 0.027$), prognostic index for NK/T-cell lymphoma (PINK) ($P = 0.026$) and types of initial treatment ($P = 0.011$) were significant prognostic factors on multivariate analysis. On Cox regression analysis, ECOG performance score ($P = 0.021$) and PINK-EBV DNA (PINK-E) ($P = 0.002$) significantly impacted on PFS; whereas ECOG performance score ($P = 0.008$) and stage ($P < 0.001$) significantly impacted on OS. For comparing CCRT ± CT and sequential CT + RT, CCRT ± CT patients ($n = 190$) were similar to sequential CT + RT patients ($n = 54$) in all evaluated clinicopathologic parameters except two significantly superior features (higher proportion of undetectable circulating EBV DNA on diagnosis and lower PINK-E scores). Despite more favorable pre-treatment characteristics, CCRT ± CT patients had CR rate, PFS and OS comparable with sequential CT + RT patients on multivariate and Cox regression analyses.

Conclusions: In stage I/II NK/T-cell lymphomas, when effective chemotherapeutic regimens were used, CCRT and sequential CT + RT gave similar outcome.

Key words: stage I/II NK/T-cell lymphomas, concurrent chemoradiotherapy, sequential chemotherapy and radiotherapy

Introduction

Natural killer (NK)/T-cell lymphomas (or extranodal NK/T-cell lymphomas, nasal type) are aggressive malignancies. Outcome is poor with conventional anthracycline-based chemotherapy (CT), including CHOP (cyclophosphamide, adriamycin, vincristine, prednisolone) or CHOP-like regimens [1]; even for stage I/II diseases with relapse rates of up to 50% [2, 3]. Radiotherapy (RT) alone is used in some centers for stage I/II NK/T-cell lymphomas [2]. However, relapse rates reached 40%–50%, usually systemically; suggesting that occult spread might have occurred [2, 3].

The observation that platinum-drugs might sensitize solid tumors to RT led to the combined use of CT (cisplatin) and RT (concurrent chemo RT, CCRT) in NK/T-cell lymphomas. In two phase II studies of stage I/II patients [4, 5], CCRT was compared with historical controls (treated with CHOP or CHOP-like regimens). CCRT apparently resulted in superior overall-response rates (ORR).

The use of nonanthracycline-containing regimens incorporating L-asparaginase has completely changed the outlook of advanced-stage NK/T-cell lymphoma [6, 7], with durable remissions achieved in 40%–50% of patients. Their use in stage I/II patients resulted in ORR of around 80% [7]. The sequential use of L-asparaginase-containing chemotherapeutic regimens followed by RT gives durable remission in up to 80% of stage I/II patients [1, 3, 7].

Because CCRT had only been evaluated against CHOP or CHOP-like regimens, its role in the era of nonanthracycline-containing regimens remains undefined. Logistically, CCRT is difficult to arrange, as RT may not be immediately available. Furthermore, CCRT causes significantly toxicity in the nasal and oral mucosae [1, 3]. Consequently, many centers adopt sequential CT (nonanthracycline-containing) and RT (CT + RT).

With the use of more effective chemotherapeutic regimens, a reappraisal of CCRT in comparison with sequential CT + RT becomes necessary. In this study, we analyzed an international cohort of patients with newly-diagnosed stage I/II NK/T-cell lymphomas, to critically evaluate CCRT versus sequential CT + RT.

Materials and methods

Patients

Cases were derived from a cohort of patients collected by an international consortium for the development of a prognostic model (prognostic index for NK/T-cell lymphoma, PINK; PINK with Epstein Barr virus, EBV, DNA, PINK-E) [8]. Briefly, patients with pathologically confirmed NK/T-cell lymphomas diagnosed between 1997 and 2013 and validated with the 2008 World Health organization classification criteria from 12 geographic regions (China, Denmark, France, Germany, Hong Kong, Japan, Malaysia, Singapore, South Korea, Sweden, Taiwan, and the USA) participating in the International NK/T-Cell Lymphoma Project were retrospectively analyzed. Inclusion criteria were newly diagnosed stage I/II disease, and treatment with nonanthracycline-containing regimens with or without RT. Approval from institutional review board of all participating centers had been obtained for the PINK/PINK-E project. For this subgroup analysis, a separate approval was not considered necessary.

Treatment

Two different CCRT protocols were employed [4, 5]. Briefly, in the Japanese protocol, 50 Gy of RT was given together with 3 cycles of two-third DeVIC (dexamethasone, etoposide, ifosfamide, carboplatin) (CCRT) [4]. In the Korean protocol, 40–52.8 Gy RT and cisplatin (30 mg/m^2/week until completion of RT) was administered, followed by three cycles of VIPD (etoposide, ifosfamide, cisplatin, dexamethasone) [5], VIDL (etoposide, ifosfamide, dexamethasone, L-asparaginase) [9] or MIDLE (methotrexate, etoposide, ifosfamide, dexamethasone, L-asparaginase) [10] post-CCRT (CCRT + CT). For patients not receiving CCRT, the protocols for RT, CT and sequential CT + RT varied. For sequential CT + RT, the general scheme was CT for 3–6 cycles, followed by involved-field RT of at least 50 Gy. A minority of patients received RT alone, or RT followed by CT.

Data analysis

Progression-free-survival (PFS) was defined as time from initial diagnosis to relapse, progression, death or last follow-up. Overall survival (OS) was defined as time from initial diagnosis to death or last follow-up. Treatment response was assessed at completion of the intended therapy, based on standard criteria adopted by participating centers relevant at the time of assessment, with no requirement mandating any specific form of imaging (computed tomography or positron emission tomography) [8]. Impact of the following parameters on complete response (CR) was analyzed by univariate analysis: gender, age, Eastern Cooperative Oncology Group (ECOG) performance score; B-symptoms; lactate dehydrogenase (LDH, normal versus elevated); Ann Arbor staging; number of extranodal sites involved (<2 versus ≥ 2); presentation circulating EBV DNA quantified by quantitative polymerase chain reaction (undetectable versus detectable); primary treatment (CT versus RT versus sequential CT + RT versus sequential RT + CT versus CCRT + CT versus CCRT); sequence of CT and RT (Korean CCRT + CT/Japanese CCRT versus CT + RT); International Prognostic Index (IPI) [11], Korean Prognostic Index (KIPI) [12], PINK (age, stage, extranodal disease, extranasal) and PINK-E (EBV-DNA) [8]. Factors significant on univariate analysis were further examined by multivariate analysis. Analysis of survivals (PFS, OS) was conducted by the Kaplan–Meier method. Potential prognostic factors (as for CR) were also analyzed for impact on survivals by univariate and multivariate analysis using Cox regression with the forward stepwise method. Two-tailed P values of <0.05 were considered as significant. All tests were carried out with the SPSS 15.0 software package (SPSS).

Results

Patients

Information on stage I/II patients was retrieved from the training cohort of the PINK/PINK-E analysis. Three hundred and forty-four patients were found. Forty-one patients were excluded (treatment before 1997, $n = 1$; insufficient data on treatment protocols, $n = 4$; insufficient follow-up data pertaining to the current study, $n = 36$). Three hundred and three patients (207 men, 96 women) at a median age 51 (18–86) years were further analyzed (Table 1) (details of patient enrollment presented in supplementary File S1, available at *Annals of Oncology* online). The majority of cases were good-risk patients (Table 1).

Treatment and outcome

Six different treatment approaches (single modality, $n = 2$; sequential modalities, $n = 2$; concurrent modalities, $n = 2$) were adopted (Table 2). CCRT were most frequent ($n = 190$) (Korean protocol, CCRT + CT; $n = 173$; Japanese protocol, CCRT, $n = 17$), followed by sequential CT + RT ($n = 54$). A minority of patients received CT alone, RT alone or sequential RT + CT.

Table 1. Clinicopathologic features of 303 stage I/II NK/T-cell lymphoma patients

Demographic and clinicopathologic features	Number (%)
Gender	
Male	207 (68%)
Female	96 (32%)
Age (median, range) (years)	51 (18–86)
Stage	
I	207 (68%)
II	96 (32%)
B symptoms	
Absent	235 (78%)
Present	68 (33%)
Eastern Cooperative Oncology Group performance score	
0	149 (49%)
1	137 (45%)
2	15 (5%)
3	1 (0.3%)
Lactate dehydrogenase	
Normal	222 (73%)
Elevated	81 (27%)
Circulating EBV DNA	
Undetectable	104 (53%)
Detectable	94 (47%)
Extranodal sites involved	
0–1	283 (93%)
>1	20 (7%)
International Prognostic Index (IPI)	
Low	257 (85%)
Low-intermediate	39 (13%)
High-intermediate	7 (2%)
Korean Prognostic index score (KIPI)	
1	148 (49%)
2	90 (30%)
3	48 (16%)
4	17 (6%)
Prognostic index for NK-cell lymphoma (PINK)	
Low	200 (66%)
Intermediate	94 (31%)
High	9 (3%)
Prognostic index for NK-cell lymphoma with EBV DNA (PINK-E)	
Low	182 (82%)
Intermediate	36 (16%)
High	4 (2%)

Table 2. Initial chemotherapy regimens administered to 303 patients with stage I/II NK/T-cell lymphomas

Treatment groups and chemotherapy regimens	Number of patients
Single modality	
Chemotherapy alone (*N*=32)	
IMEP	12
SMILE	11
VIDL	3
L-Asparaginase based	3
VIPD	1
Others	2
Radiotherapy alone (*N*=18)	
Nil	18
Sequential modalities	
Sequential chemotherapy and radiotherapy (*N*=54)	
SMILE	18
IMEP	13
L-Asparaginase-containing regimens[a]	8
ICE	5
Gemcitabine-containing regimens[b]	5
ESHAP	1
DEVIC	1
Others	3
Sequential radiotherapy and chemotherapy (*N*=9)	
ICE	4
IMEP	3
Others	2
Concurrent modalities	
Concomitant chemoradiotherapy (Korean protocol)±chemotherapy (*N*=173)	
Cisplatin (with radiotherapy)+VIPD/VIDL/MIDLE	173
Concomitant chemoradiotherapy (Japanese protocol) (*N*=17)	
Two-third DeVIC	17

[a]Predominantly L-asparaginase, methotrexate, dexamethasone, with one case containing gemcitabine.
[b]Gemcitabine in combination with oxaliplatin with or without methotrexate.
SMILE, dexamethasone, methotrexate, ifosfamide, L-asparaginase, etoposide; VIPD, etoposide, ifosfamide, cisplatin, dexamethasone; VIDL, etoposide, ifosfamide, dexamethasone, L-asparaginase; IMEP, ifosfamide, methotrexate, etoposide, prednisolone; ICE, ifosfamide, carboplatin, etoposide; ESHAP, etoposide, methylprednisolone, cytarabine, cisplatin; MIDLE, methotrexate, ifosfamide, dexamethasone, L-asparaginase, etoposide; DeVIC, dexamethasone, etoposide, ifosfamide, carboplatin.

All CT protocols were nonanthracycline containing (Table 2). Two hundred and forty patients (79%) achieved CR (Table 3).

Prognostic factors impacting on response

Univariate analysis showed that CR was significantly associated with stage ($P<0.001$), B symptoms ($P=0.02$), ECOG performance score ($P=0.041$), LDH ($P=0.009$), KIPI ($P=0.002$), PINK ($P=0.016$), initial treatment ($P<0.001$), and the sequence of CT and RT ($P=0.02$). On multivariate analysis, stage ($P=0.027$), PINK ($P=0.026$), and initial treatment ($P=0.011$) remained significantly associated with CR (Table 3).

Prognostic factors impacting on PFS

The PFS of the entire cohort was shown in Figure 1A. PFS was significantly associated with ECOG performance score ($P<0.001$), LDH ($P=0.013$), stage ($P<0.001$), presentation circulating EBV DNA ($P=0.02$), initial treatment ($P<0.001$), sequence of CT and RT ($P=0.035$), IPI ($P=0.003$), KIPI ($P=0.01$), PINK ($P<0.001$), and PINK-E ($P<0.001$) (Table 4) (Figure 1B–J) (PFS curves for nonsignificant parameters could be found in

Table 3. Prognostic impact of demographic and clinicopathologic features on response in 303 stage I/II NK/T-cell lymphoma patients

Demographic and clinicopathologic features	CR	Non-CR	*P* value	
			Univariate	Multivariate
Gender				
Male	163	44		
Female	77	19	0.770	–
Age (years)	51.6	52.6	0.66	–
Stage				
I	176	31		
II	64	32	<0.001	0.027
B symptoms				
Absent	193	42		
Present	47	21	0.02	NS
ECOG performance score				
0	125	24		
1	105	32		
2	9	6		
3	1	0	0.041	NS
Lactate dehydrogenase				
Normal	184	38		
Elevated	56	25	0.009	NS
Extranodal sites involved				
<2	227	56		
≥2	13	7	0.11	–
Presentation circulating EBV DNA				
Undetectable	89	15		
Detectable	77	17	0.485	–
International Prognostic Index				
Low	206	51		
Low-intermediate	29	10		
High-intermediate	5	2	0.621	–
Korean prognostic index				
1	126	22		
2	70	20		
3	36	12		
4	8	9	0.002	NS
Prognostic index for NK/T-cell lymphoma (PINK)				
Low	168	32		
Intermediate	66	28		
High	6	3	0.016	0.026
PINK EBV DNA (PINK-E)				
Low	156	26		
Intermediate	27	9		
High	3	1	0.250	–
Primary treatment				
Chemotherapy	13	19		
Radiotherapy	13	5		
Sequential chemotherapy+radiotherapy	41	13		
Concurrent chemoradiotherapy+chemotherapy (Korean protocol)	157	16		
Sequential radiotherapy+chemotherapy	5	4		
Concurrent chemoradiotherapy (Japanese protocol)	11	6	<0.001	0.011
Subgroup analysis of primary treatment				
Concurrent chemoradiotherapy (Korean+Japanese protocols)	168	22		
Sequential chemotherapy+radiotherapy	41	13	0.020	NS

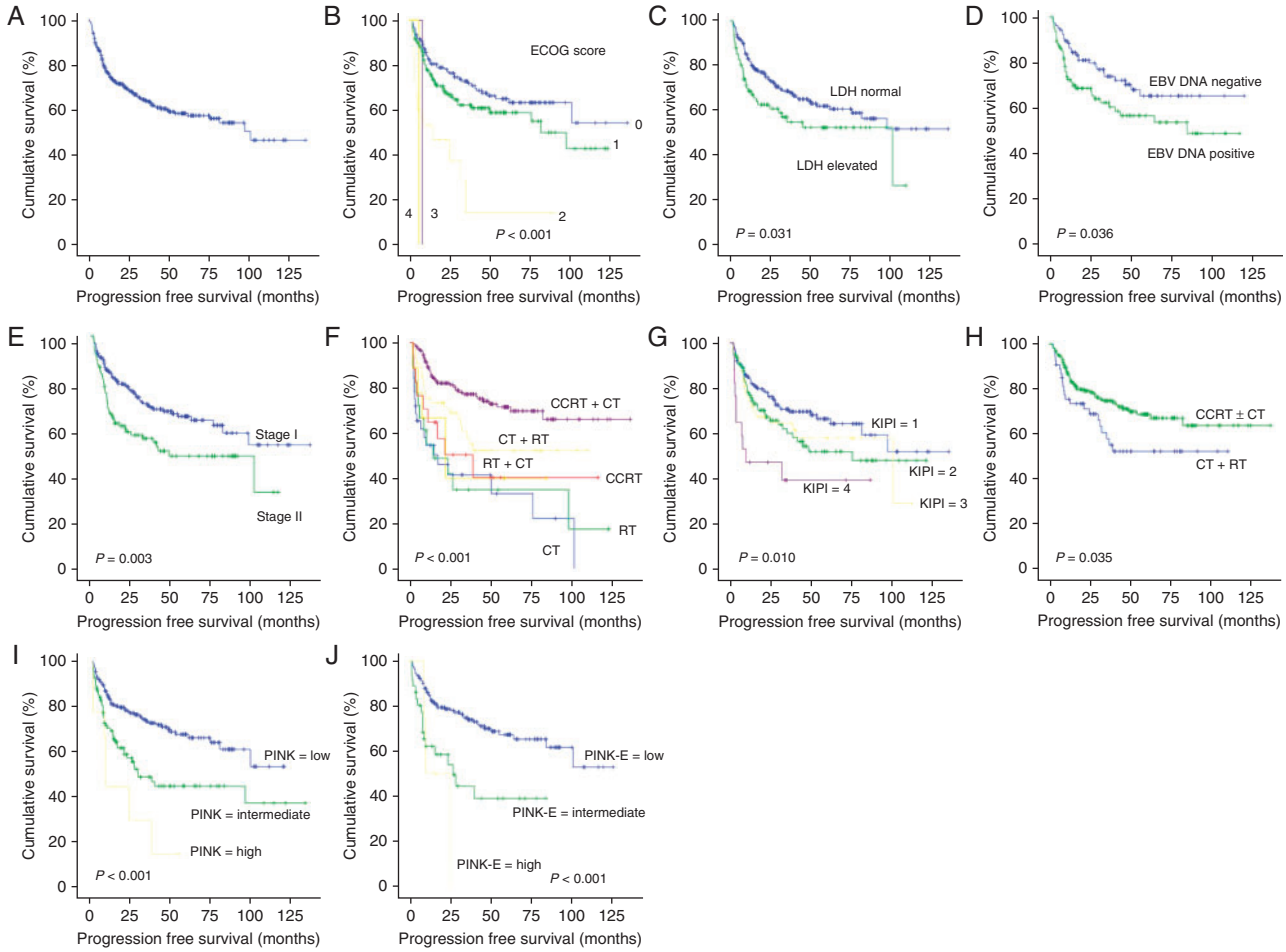

Figure 1. Progression-free survivals of 303 patients with stage I/II NK/T-cell lymphoma. (A) PFS of the entire cohort. (B–J) Significant factors that impacted on PFS on univariate analysis. On multivariate analysis, only ECOG performance score (B) and PINK-E (J) remained significant.

Table 4. Prognostic factors impacting on survivals of stage I/II NK/T-cell lymphomas

	P value			
Parameters	**Univariate**	**Multivariate**	**Hazard ratio**	**95% CI**
Progression-free survival				
ECOG performance score	<0.001	0.021	1.673	1.081–2.589
LDH	0.031	–		
Stage	<0.003	–		
Presentation circulating EBV DNA	0.036	–		
Types of initial treatment	<0.001	–		
Sequence of chemotherapy and radiotherapy	0.035	–		
IPI	0.003	–		
KIPI	0.01	–		
PINK	<0.001	–		
PINK-E	<0.001	0.002	2.378	1.378–4.097
Overall survival				
ECOG performance score	<0.001	0.008	1.628	1.133–2.340
Stage	<0.001	<0.001	2.995	1.635–5.488
Types of initial treatment	<0.001	–		
KIPI	0.015	–		
PINK	0.036	–		

CI, confidence interval; –, not significant; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; IPI, International Prognostic Index; KIPI, Korean Prognostic Index; PINK, Prognostic Index for NK/T-cell lymphoma; PINK-E, PINK with EBV DNA.

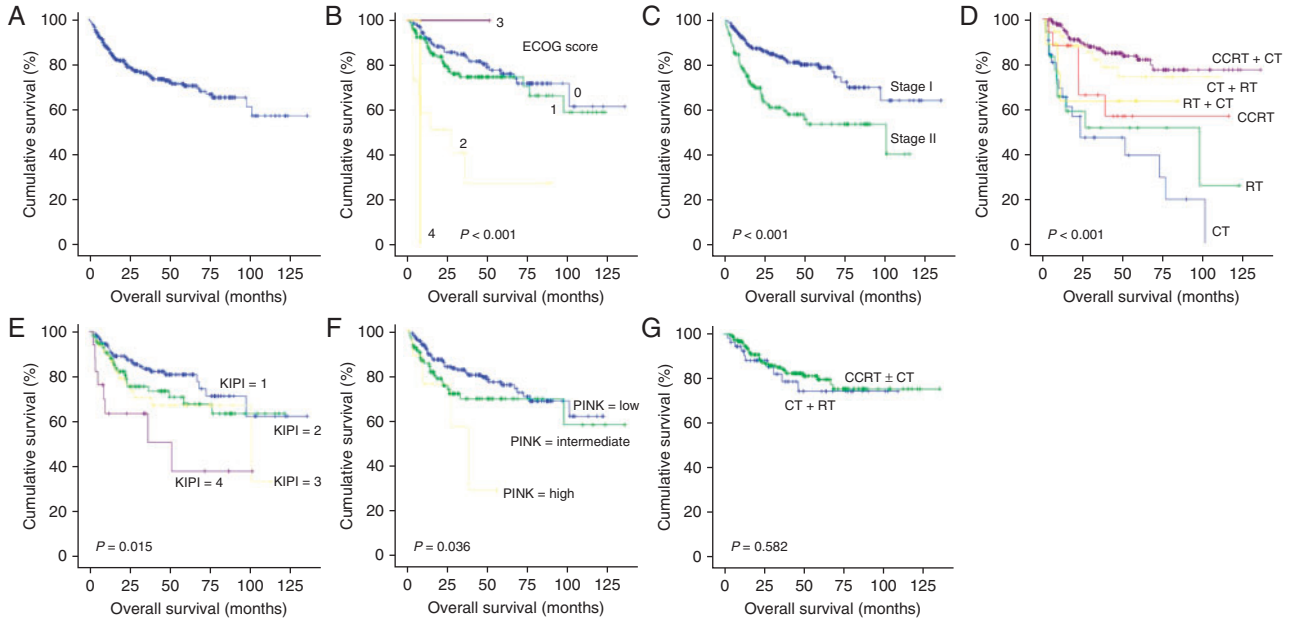

Figure 2. Overall survivals of 303 patients with stage I/II NK/T-cell lymphoma. (A) OS of the entire cohort. (B–F) Significant factors that impacted on OS on univariate analysis. On multivariate analysis, only ECOG performance score (B) and stage (C) remained significant. (G) The OS of patients receiving CCRT and sequential CT + RT were almost identical.

supplementary File S2, available at *Annals of Oncology* online). On Cox-regression analysis, significant prognostic factors included ECOG performance score ($P = 0.021$; hazard ratio: 1.673; 95% confidence interval: 1.081–2.589) and PINK-E ($P = 0.002$; hazard ratio: 2.378; 95% confidence interval: 1.378–4.097) (Table 4).

Prognostic factors impacting on OS

The OS of the entire cohort was shown in Figure 2A. OS was significantly associated with ECOG performance score ($P < 0.001$), stage ($P < 0.001$), initial treatment ($P < 0.001$), KIPI ($P = 0.015$), and PINK ($P = 0.036$) (Table 4) (Figure 2B–F) (OS curves for nonsignificant parameters could be found in supplementary File S2, available at *Annals of Oncology* online). On Cox-regression analysis, significant prognostic factors included ECOG performance score ($P = 0.008$; hazard ratio: 1.628; 95% confidence interval: 1.133–2.340) and stage ($P < 0.001$; hazard ratio: 2.995; 95% confidence interval: 1.635–5.488) (Table 4).

Comparison between CCRT and sequential CT + RT

Patients receiving CCRT (Korean CCRT + CT and Japanese CCRT, $n = 190$) and sequential CT + RT ($n = 54$) were similar in conventional clinicopathologic features (Table 5). However, CCRT patients showed two more favorable features, including undetectable presentation circulating EBV DNA (58% versus 21%, $P = 0.002$), and lower PINK-E scores ($P < 0.001$). For patients treated with sequential CT + RT, 83% received regimens previously shown to have high efficacies in NK/T-cell lymphomas (dexamethasone, methotrexate, ifosfamide, L-asparaginase, etoposide, SMILE [6, 7], $n = 18$; ifosfamide, methotrexate, etoposide, prednisolone, IMEP [13], $n = 13$; L-asparaginase-containing regimens [1–3], $n = 8$; gemcitabine-containing regimens [1–3], $n = 5$; DeVIC [4], $n = 1$); and 11% received regimens more intensive than conventional anthracycline-containing regimens (ifosfamide, carboplatin, etoposide, ICE, $n = 5$; etoposide, methylprednisolone, cytarabine, cisplatin, $n = 1$) (Table 4). On univariate analysis, CCRT resulted in a higher CR rate (Table 3), but this difference was not found on multivariate analysis. In survival analysis, CCRT was associated with a better PFS (Figure 1H), but this difference disappeared on multivariate analysis. In OS analysis, the survival curves of CCRT and sequential CT + RT almost overlapped, plateauing at 72%–74% after 5 years (Figure 2G).

Discussion

Current controversies on stage I/II NK/T-cell lymphomas center on the relative importance of RT and CT [14], and how they should be sequenced [1, 3]. Considerable institutional bias exists [4, 7]. Risk-stratification models have been proposed for stage I/II patients [15], predicated on the notion that low-risk patients can receive RT alone, whereas high-risk patients should receive RT and CT. However, these prognostic models have not been validated prospectively.

Frontline CCRT combines early RT with CT, harnessing the advantages of both approaches in stage I/II patients [5, 6]. Chemotherapies used in CCRT protocols are more effective than anthracycline-containing regimens. Therefore, it is unclear if the superiority of CCRT over anthracycline-containing regimens as detected in previous phase II studies [4, 5] was due to the CT or the chemo RT part of the CCRT.

We included a minority of cases treated with CT or RT alone, so that patient disposition could be clearly presented. Their outcome was poor, suggesting that these approaches were adopted not based on a perceived small tumor volume. Although

Table 5. Comparison of stage I/II NK/T-cell lymphoma patients receiving concurrent chemoradiotherapy (CCRT) or sequential chemotherapy and radiotherapy (CT + RT)

Demographic and clinicopathologic features	CCRT (N = 190)	CT + RT (N = 54)	*P* value
Gender			
Male	126	38	
Female	64	16	NS (0.575)
Age	52.6	50.4	NS (0.288)
Stage			
I	132	38	
II	58	16	NS (0.899)
B symptoms			
Absent	150	39	
Present	40	15	NS (0.297)
ECOG performance score			
0	95	31	
1	91	20	
2	3	3	
3	1	0	NS (0.210)
Lactate dehydrogenase			
Normal	145	38	
Elevated	45	16	NS (0.373)
Extranodal sites involved			
< 2	180	51	
≥ 2	10	3	NS (0.933)
Presentation circulating EBV DNA			
Undetectable	90	4	
Detectable	65	15	0.002
International Prognostic Index			
Low	169	45	
Low-intermediate	19	7	
High-intermediate	2	2	NS (0.317)
Korean Prognostic Index			
1	96	26	
2	55	14	
3	33	9	
4	6	5	NS (0.300)
Prognostic index for NK/T-cell lymphoma (PINK)			
Low	129	36	
Intermediate	58	16	
High	3	2	NS (0.623)
PINK EBV DNA (PINK-E)			
Low	151	13	
Intermediate	22	6	
High	0	2	<0.001

NS, not significant.

treatment groups were rather numerous, our main observation was the comparison of CCRT with sequential CT + RT. The key difference between our analysis and reported results of CCRT versus CT (CHOP or CHOP-like) [4, 5] was that 94% of our sequential CT + RT patients received regimens that either have already been shown effective in NK/T-cell lymphomas (SMILE, IMEP, DeVIC, L-asparaginase-containing, gemcitabine-containing) or were more intensive (ICE, ESHAP) than anthracycline-containing regimens. Our results showed that when effective CT regimens were used, sequential CT + RT had the same OS as CCRT. The CR rate and PFS of patients receiving CCRT appeared superior. However, it must be noted that CCRT patients had lower disease risks (lower tumor load as reflected by higher frequency of undetectable presentation EBV DNA; and lower PINK-E scores). These lower disease risks might account for the apparently superior CR rate and PFS of CCRT. In fact, this was fully reflected in multivariate analysis of CR rate and PFS, where a significant difference between CCRT and sequential CT + RT was not observed. Therefore, the apparently better CR rate and PFS in the CCRT group were due to inherent patient characteristics and not the impact of treatment.

Although our study is retrospective, being a multicenter analysis adds strength to its findings. Patients were treated in more than ten geographic regions. Furthermore, CCRT involved two different approaches; whereas in sequential CT + RT, more than eight different regimens were employed. Given such diversities, it is remarkable that the OS of CCRT and sequential CT + RT almost overlapped, which is a robust proof that these two approaches give similar outcome. Hence, the previously reported advantage of CCRT over CT and RT [4, 5] could be attributed to ineffective CT in the latter approach.

Sequential CT + RT has important advantages over CCRT. To expedite treatment, CT is more readily available than immediate RT. Secondly, CCRT causes significant mucosal damage and impairs nutritional status. Thirdly, in sequential CT + RT, most patients would have reached a remission before RT, greatly increasing their tolerability to irradiation. Finally, with a regimen such as SMILE, ~75% of patients could achieve CR on interim positron emission tomography (Deauville score ≤ 3) [16]. The remaining patients not achieving satisfactory response at interim can still benefit from RT.

Our observations have important implications on the treatment of stage I/II patients. With either CCRT or sequential CT + RT, the OS curve plateaued at 72%–75% after 5 years. Therefore, the argument is no longer which of RT or CT is superior, nor how RT and CT should be sequenced [14]. Instead, efforts should now be dedicated to defining how the other 25% of cases can be cured. Stage II disease and high-risk PINK/PINK-E scores portend poor survivals, and further research is needed to optimally treat stage I/II patients with these risks.

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Disclosure

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