Retrospective analysis of clinical characteristics, treatment outcomes and prognosis of patients with natural killer/T-cell lymphoma

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Abstract. Natural killer/T-cell lymphoma (NKTCL) is the most common T-cell non-Hodgkin lymphoma in China; however, the clinical characteristics and optimal treatment remain unclear. The present study aimed to retrospectively assess the clinical features of patients with NKTCL and to determine treatment strategies. A total of 200 patients who were diagnosed with NKTCL and admitted to the Cancer Center, Union Hospital (Wuhan, China) between June 2013 and June 2022 were identified. Clinical data from these patients were collected and analyzed to evaluate the clinical features, treatment outcomes and prognostic factors. A total of 171 patients diagnosed with NKTCL were ultimately enrolled. Patients were diagnosed at a median age of 45 years and had a male-to-female ratio of 2:1. Out of the 171 patients, 117 were in the early stage (stage I/II; 68.4%) and 54 were in the advanced stage (stage III/IV; 31.6%) of NKTCL. Among these patients, B symptoms were present in 60.2% of patients (103/171) and the Eastern Cooperative Oncology Group performance status was scored as 0-1 in 93.6% of patients (160/171). Most patients had a low-to-moderate risk of international prognostic index (147/171; 86.0%), prognostic index for NKTCL (PINK; 122/171; 71.3%) and PINK with extended features (112/171; 65.5%). At baseline, it was demonstrated that Epstein-Barr virus DNA was positive in the serum of 166/171 patients (2.9%). Combined chemotherapy and radiotherapy at 54 Gy revealed a promising effect with the highest overall response rate (ORR) of 98.2%, a 4-year progression-free survival (PFS) rate of 82.5% [95% confidence interval (CI), 75.1-89.9%] and an overall survival (OS) rate of 92.2% (95% CI, 86.9-97.5%) for the early-stage group. Pegasparase-based chemotherapy was used to treat advanced-stage patients, resulting in a 4-year PFS rate of 62.3% (95% CI, 47.4-77.2%) and an OS rate of 63.5% (95% CI, 48.2-78.8%). The regimen containing the programmed cell death protein 1 inhibitor camrelizumab demonstrated an ORR of 100% in both the early- and advanced-stage cohorts. Moreover, stage and an age of >60 years were independent prognostic factors for poor PFS, whilst stage and elevated lactate dehydrogenase were independent prognostic factors for poor OS. In conclusion, the results indicated promising efficacy for pegaspargase-based chemotherapy in terms of response rates and survival outcomes for both early- and advanced-stage patients. However, further refinement of treatment strategies is needed.

Introduction

Natural killer/T-cell lymphoma (NKTCL) represents a rare and highly aggressive subtype of non-Hodgkin lymphoma (NHL) with Epstein-Barr virus (EBV) infection. The incidence of NKTCL exhibits a predilection for certain geographical regions, such as Asia and Latin America, with relatively fewer cases reported in Europe and North America. Within the Chinese population, NKTCL accounts for 12-17% of NHL cases and 55-61% of peripheral T-cell lymphoma cases (1,2).

The therapeutic strategies for NKTCL vary based on disease staging, and no standard regimen has been established. Combined radiotherapy (RT) and chemotherapy are recommended for patients with early-stage (Ann Arbor stage I/II) (3) disease, but systemic therapy is recommended for patients with advanced-stage disease (4,5). The success of early-stage NKTCL treatment hinges upon the irradiation field and dosage, which are associated with local control rates and prognosis (6). The optimal chemotherapy regimens for NKTCL include those

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incorporating pegaspargase, such as SMILE (dexamethasone, methotrexate, ifosfamide, L-asparaginase and etoposide) (7), P-Gemox (gemcitabine, pegaspargase and oxaliplatin) (8), P-GDP (dexamethasone, cisplatin, gemcitabine and pegaspargase) (9) and AspMetDex (L-asparaginase, methotrexate and dexamethasone) regimens (10). Largely variable effective results have been reported for these regimens (11); however, a standard treatment for NKTCL has not been established.

Several prognostic models have been developed for patients with NKTCL. For example, the international prognostic index (IPI) and Korean Prognostic Index are useful for patients with anthracycline-containing response (12), and the prognostic index for NKTCL (PINK) and the prognostic index for NKTCL with extended features (PINK-E) were developed for patients treated with non-anthracycline-containing regimens (13,14). However, the most accurate model is yet to be determined.

The present study performed a retrospective analysis of patients with NKTCL who received treatment at the Cancer Center, Union Hospital, Huazhong University of Science and Technology (Wuhan, China) between June 2013 and June 2022. The aim was to assess the clinical features, treatment outcomes and prognostic factors of NKTCL, thereby contributing to a deeper understanding of this aggressive disease.

Materials and methods

Patients. Patients diagnosed with NKTCL between June 2013 and June 2022 at the Cancer Center Union Hospital, Huazhong University of Science and Technology, were identified, and those that met the following criteria were included: i) Histologically confirmed NKTCL according to the World Health Organization Classification of Tumors of Hematopoietic and Lymphoid Tissues (15); ii) ≥1 type of antitumor therapy administered; and iii) follow-up completed and clinical data available. The sample size was determined by the total number of eligible cases meeting the inclusion criteria during this period. The clinical data were retrieved from electronic medical records, including sex, age, Eastern Cooperative Oncology Group performance status (ECOG PS) (16), disease staging, involved anatomical sites, lactate dehydrogenase (LDH) levels, prognostic indicators, EBV DNA levels, hematological characteristics, presence of B symptoms and radiological manifestations.

The present study was approved by the Ethics Committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology (approval no. 20240986). Written informed consent was waived, as there were no conflicts of interest or potential harm to patients, and the confidentiality of patient data was guaranteed in accordance with the requirements of the Ethics Committee.

Treatments. Treatment strategies were implemented based on the stage classification of each patient. For those presenting with early-stage disease, a radiation regimen consisting of 50-54 Gy delivered over 25-27 fractions was administered concurrently with weekly intravenous cisplatin at a dose of 30 mg/m^2. Following completion of radiation therapy, patients underwent 3-4 cycles of pegaspargase-based chemotherapy (dosing schedule as described for those with advanced-stage disease).

By contrast, patients diagnosed with advanced-stage disease received chemotherapy as the primary treatment modality. The selection of chemotherapy regimens was determined in alignment with the patient's individual preferences. The combined chemotherapy protocols employed included PIDE (2,500 IU/m^2 pegaspargase with a maximum dose of 3,750 IU administered intramuscularly on day 1; $1g/m^2$ ifosfamide administered intravenously on days 2-4; 40 mg dexamethasone administered orally on days 1-4; and 100 mg/m^2 etoposide administered intravenously on days 2-4), P-GDP (2,500 IU/m^2 pegaspargase with a maximum dose of 3,750 IU administered intramuscularly on day 1; 1,000 mg/m^2 gemcitabine administered intravenously on days 1-8; 40 mg dexamethasone administered orally on days 1-4; and 25 mg/m^2 cisplatin administered intravenously on days 1-3), P-Gemox (2,500 IU/m^2 pegaspargase administered intramuscularly on day 1; 1,000 mg/m^2 gemcitabine administered intravenously on days 1-8; and 100 mg/m^2 oxaliplatin administered intravenously on days 1-8) and PPME (2,500 IU/m^2 pegaspargase administered intramuscularly on day 1; 100 mg/m^2 etoposide administered intravenously on days 1-3; 3 g/m^2 high-dose methotrexate administered intravenously on day 4; and 200 mg camrelizumab administered intravenously on day 7). The chemotherapy cycles were repeated every 21 days. Regimens were designed by investigators based on prior literature (6-9), with P-Gemox, PIDE and P-GDP adapted from pegaspargase-based protocols and PPME incorporating immune checkpoint blockade to reflect immunotherapy advances. Response evaluation was performed following the completion of RT or after every two cycles of chemotherapy.

Statistical analysis. The statistical analyses were performed using SPSS 26.0 software (IBM Corp.) and GraphPad Prism 9 software (Dotmatics). Pearson's χ^2 test was used for comparing data from different groups. Kaplan-Meier curves and the log-rank test were used to evaluate OS and PFS. To assess prognostic factors associated with OS and PFS, Cox proportional hazards regression was employed. Both univariate and multivariate Cox analyses were performed to identify variables with significant prognostic values. To account for multiple comparisons, the Benjamini-Hochberg false discovery rate correction was applied separately to P-values from multivariate Cox models for PFS and OS. Furthermore, an interaction effect analysis was performed using R software (version 4.3.2; Posit Software, PBC). Specifically, Cox proportional hazards regression models (survival package) were fitted for both PFS and OS, and multiplicative interaction terms (stage x age, stage x LDH, stage x EBV DNA level and EBV DNA x age) were included in the multivariate models. Wald tests were applied to evaluate the statistical significance of the interaction terms, and hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated. For the retrospective sample size, an events per covariate value of 5-10 was targeted to ensure reliable multivariate Cox model estimates for PFS and OS, with sufficient power to detect a hazard ratio of 2.0 (α=0.05). $P<0.05$ was considered to indicate a statistically significant difference.

Results

Characteristics of patients. A retrospective analysis was performed on 200 individuals newly diagnosed with NKTCL who were admitted to the Cancer Center at Union Hospital between June 2013 and June 2022. Among the initial cohort, 29 patients were excluded from the study: 12 individuals did not undergo any form of treatment, whilst 17 received inadequate treatment. A total of 171 patients were subsequently included in the final analysis. Within this cohort, there were 114 male patients (66.7%) and 57 female patients (33.3%), resulting in a male-to-female ratio of 2:1. The mean age of the patients was 45 years, with an age range of 16-77 years. The distribution of disease stages revealed that 117 patients presented with early-stage disease (stage I/II; 68.4%), whilst 54 patients were classified as having advanced-stage disease (stage III/IV; 31.6%). Among the patient population, 60.2% (103/171) exhibited B symptoms, whilst elevated LDH levels were observed in 19.3% of patients (33/171). ECOG PS scores of 0-1 were recorded for 93.6% of individuals (160/171). Additionally, most patients were categorized as having a low-to-moderate risk based on the IPI (86.0%; 147/171), PINK (71.3%; 122/171) and PINK-E scores (65.5%; 112/171). Notably, baseline assessments revealed the presence of EBV DNA in the bloodstream of all patients except for 5 individuals (2.9%). A detailed summary of the clinical characteristics of the patient cohort is provided in Table I.

Table I. Clinical characteristics of patients with natural killer/T-cell lymphoma (n=171).

Characteristics	Patients, n (%)
Sex	
Male	114 (66.7)
Female	57 (33.3)
Age, years	
≥60	33 (19.3)
<60	138 (80.7)
B symptoms	
Yes	103 (60.2)
No	68 (39.8)
Distant lymph node involvement	
Yes	49 (28.7)
No	122 (71.3)
LDH	
Elevated	33 (19.3)
Normal	138 (80.7)
Ann Arbor Stage	
I/II	117 (68.4)
III/IV	54 (31.6)
Bone marrow involvement	
Yes	18 (10.5)
No	153 (89.5)
ECOG PS	
0-1	160 (93.6)
≥2	11 (6.4)
IPI	
0-2	147 (86.0)
3-5	24 (14.0)
PINK	
0-2	122 (71.3)
3-5	49 (28.7)
PINK-E	
0-2	114 (66.7)
3-5	57 (33.3)
Baseline serum EBV DNA	
Positive	106 (62.0)
Negative	65 (38.0)

NKTCL, natural killer/T-cell lymphoma; LDH, lactate dehydrogenase; ECOG PS, Eastern Cooperative Oncology Group performance status; IPI, International Prognostic Index; PINK, prognostic index for NKTCL; PINK-E, prognostic index for NKTCL with extended features; EBV, Epstein-Barr virus.

Treatment responses

Treatment response in patients with early-stage NKTCL. A total of 117 patients diagnosed with early-stage NKTCL were treated with combined RT and chemotherapy. The ORR achieved through this combined treatment approach was 98.2%. In terms of the chemotherapy regimens employed, the patient cohort was stratified as follows: 66 individuals (56.4%) were subjected to the PIDE protocol, 27 patients (23.1%) received P-GDP, 13 patients (11.1%) were treated with the PPME and 11 patients (9.4%) underwent P-Gemox treatment. Notably, patients administered PIDE and PPME exhibited an ORR of 100%, whilst those receiving P-GDP and P-Gemox demonstrated response rates of 96.4 and 90.9%, respectively. Detailed findings pertaining to treatment responses are presented in Table II.

Treatment response in patients with advanced-stage NKTCL. A total of 54 patients diagnosed with advanced-stage NKTCL were subjected to chemotherapy, either as a standalone treatment or in combination with RT. The choice of treatment modality was made in consultation with each patient, considering individual preferences. The ORR achieved through these interventions was determined to be 92.5%. In terms of the specific chemotherapy regimens employed, patient management encompassed the following strategies: 17 individuals (31.5%) underwent treatment with PPME, 13 patients (24.1%) were administered P-GDP, 12 patients (22.2%) received PIDE, 8 individuals (14.8%) were treated with P-Gemox, 3 patients (5.6%) received AspaMetDex and 1 patient (1.9%) was enrolled in a clinical trial. A total of 18 patients underwent RT after completing the chemotherapy regimen. Notably, patients managed with PPME exhibited an ORR of 100%, with a complete response (CR) rate of 94.1%. Those subjected to P-GDP demonstrated an ORR of 92.3%, whilst individuals receiving PIDE achieved an ORR of 100%. Patients treated with P-Gemox exhibited an ORR of 87.5%, whilst those receiving AspaMetDex demonstrated an ORR of 66.7%. The sole patient participating in the clinical trial experienced

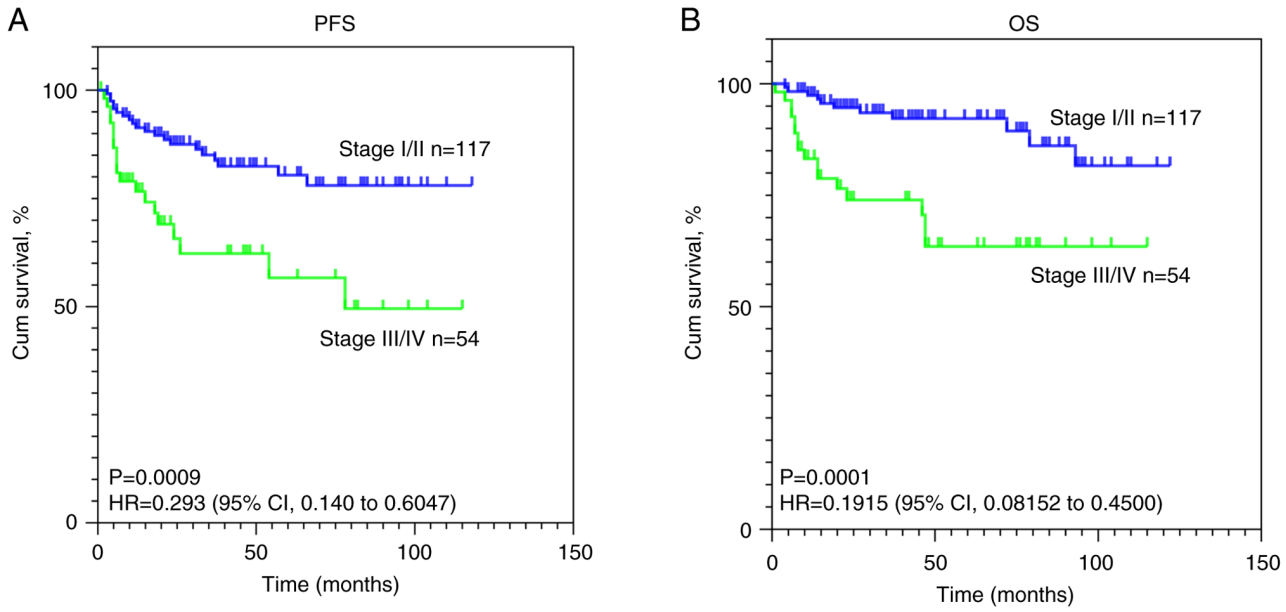

Figure 1. Kaplan-Meier survival curves of (A) PFS and (B) OS stratified by disease stage at diagnosis. Patients with early-stage disease (stage I-II) demonstrated significantly longer PFS and OS times compared with those with advanced-stage disease (stage III-IV), highlighting the prognostic impact of tumor stage in natural killer/T-cell lymphoma. HR, hazard ratio; PFS, progression-free survival; OS, overall survival; cum, cumulative; CI, confidence interval.

Table II. Treatment response in patients with early-stage natural killer/T-cell lymphoma.

Treatment	CR, n (%)	PR, n (%)	SD, n (%)	PD, n (%)
PIDE (n=66)	66 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
P-GDP (n=27)	26 (96.3)	0 (0.0)	0 (0.0)	1 (3.7)
PPME (n=13)	13 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gemox (n=11)	10 (90.9)	0 (0.0)	0 (0.0)	1 (9.1)

PIDE, pegaspargase, ifosfamide, dexamethasone and etoposide; P-GDP, pegaspargase, gemcitabine, dexamethasone and cisplatin; PPME, pegaspargase, etoposide, high-dose methotrexate and camrelizumab; P-Gemox, pegaspargase, gemcitabine and oxaliplatin; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Table III. Treatment response in patients with advanced-stage natural killer/T-cell lymphoma.

Treatment	CR, n (%)	PR, n (%)	SD, n (%)	PD, n (%)
PPME (n=17)	16 (94.1)	1 (5.9)	0 (0.0)	0 (0.0)
P-GDP (n=13)	12 (92.3)	0 (0.0)	1 (7.7)	0 (0.0)
PIDE (n=12)	12 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
P-Gemox (n=8)	7 (87.5)	0 (0.0)	1 (12.5)	0 (0.0)
AspaMetDex (n=3)	2 (66.7)	0 (0.0)	0 (0.0)	1 (33.3)

PPME, pegaspargase, etoposide, high-dose methotrexate and camrelizumab; P-GDP, pegaspargase, gemcitabine, dexamethasone and cisplatin; PIDE, pegaspargase, ifosfamide, dexamethasone and etoposide; P-Gemox, pegaspargase, gemcitabine and oxaliplatin; AspaMetDex, pegaspargase, methotrexate and dexamethasone; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

progressive disease. Detailed findings regarding treatment responses are presented in Table III.

Survival outcomes. Over a median follow-up period of 47.5 months (range, 2-122 months), the mortality rate among patients was 15.8% (27/171). Of these cases, 26 deaths were attributed to disease progression, whilst 1 patient death was associated with an infection. Among the deceased, 11 patients were in the early-stage category (11/117; 9.4%) and 16 were classified as advanced-stage patients (16/54; 29.6%). A total of 39 patients experienced disease progression, accounting for 22.8% of the total patient cohort. Specifically, 20 cases of disease progression were observed within the early-stage group (20/117; 17.1%) and 19 instances were recorded among the advanced-stage patients (19/54; 35.2%). The 4-year PFS and OS rates for the entire patient cohort were 76.7% (95% CI, 69.8-83.6%) and 83.3% (95% CI, 77.1-89.6%), respectively. Furthermore, the 4-year PFS rate was 82.5% (95% CI, 75.1-89.9%) for patients in the early-stage group and 62.3% (95% CI, 47.4-77.2%) for those in the advanced-stage group. The 4-year OS rate was recorded as 92.2% (95% CI, 86.9-97.5%) for the early-stage patients and 63.5% (95% CI, 48.2-78.8%) for the advanced-stage cohort. Kaplan-Meier estimates of PFS and OS are visually depicted in Fig. 1. The statistical analysis using the log-rank test indicated significant differences in survival curves (both P<0.001) for both OS and PFS based on stage.

To determine if treatment regimen choice influenced survival outcomes in NKTCL, Kaplan-Meier survival curves were generated for four chemotherapy regimens (P-Gemox, PIDE, P-GDP and PPME) and compared using log-rank

Table IV. Univariate analysis of prognosis factors associated with survival.

Factors	PFS		OS	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Sex (male vs. female)	1.249 (0.655-2.383)	0.499	1.193 (0.546-2.607)	0.658
Age (>60 vs. ≤60 years)	9.352 (1.284-68.121)	0.027[a]	1.293 (0.447-3.740)	0.636
Stage (I/II vs. III/IV)	0.362 (0.192-0.677)	0.002[a]	0.251 (0.116-0.544)	<0.001[a]
ECOG PS (0/1 vs. ≥2)	0.910 (0.279-2.965)	0.876	0.597 (0.179-1.989)	0.401
B symptoms (no vs. yes)	0.729 (0.374-1.420)	0.353	0.623 (0.273-1.424)	0.262
LDH (≤240 vs. >240 IU/l)	0.662 (0.314-1.395)	0.278	0.227 (0.105-0.493)	<0.001[a]
EBV DNA levels (<400 vs. ≥400 copies/ml)	0.669 (0.344-1.304)	0.802	0.313 (0.118-0.827)	0.019[a]
Chemotherapy regimen	-	0.053	-	0.297
PGDP vs. PIDE	1.771 (0.697-4.504)	0.230	1.697 (0.565-5.098)	0.346
PGDP vs. P-Gemox	2.914 (0.944-8.997)	0.063	3.611 (1.005-12.97)	0.051
PGDP vs. PPME	3.431 (1.196-9.841)	0.052	2.500 (0.685-9.118)	0.165

[a]P<0.05. PFS, progression-free survival; OS, overall survival; HR, hazard ratio; LDH, lactate dehydrogenase; ECOG PS, Eastern Cooperative Oncology Group performance status; EBV, Epstein-Barr Virus; PPME, pegaspargase, etoposide, high-dose methotrexate and camrelizumab; P-GDP, pegaspargase, gemcitabine, dexamethasone and cisplatin; PIDE, pegaspargase, ifosfamide, dexamethasone and etoposide; P-Gemox, pegaspargase, gemcitabine and oxaliplatin.

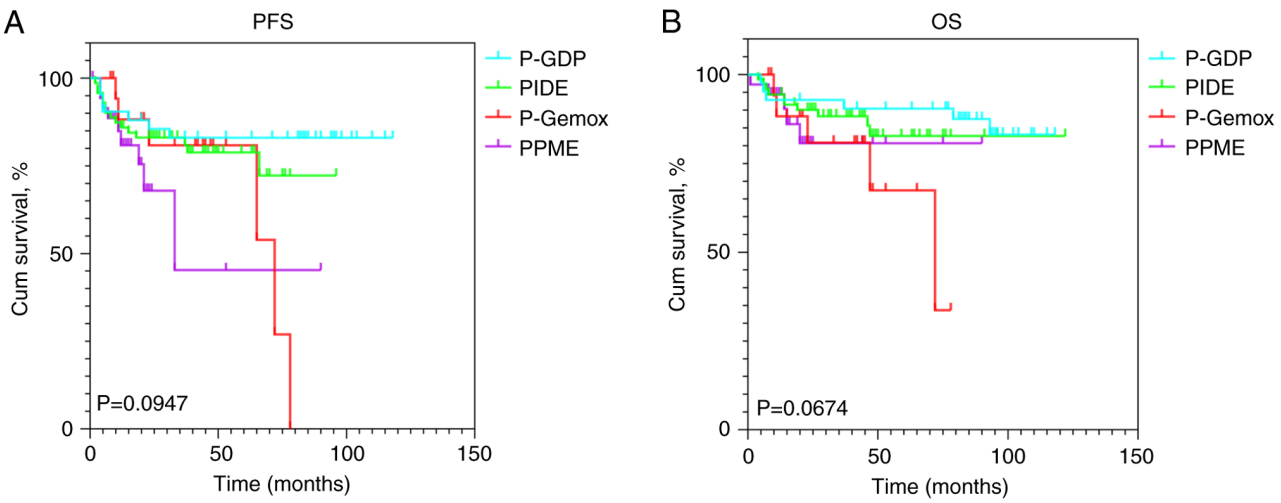

Figure 2. Kaplan-Meier survival curves of (A) PFS and (B) OS stratified by chemotherapy regimens, including PIDE, P-GDP, P-Gemox and PPME. P-GDP, pegaspargase, gemcitabine, dexamethasone, and cisplatin; PIDE, pegaspargase, ifosfamide, dexamethasone, and etoposide; P-Gemox, pegaspargase, gemcitabine, and oxaliplatin; PPME: pegaspargase, etoposide, high-dose methotrexate, and camrelizumab; PFS, progression-free survival; OS, overall survival; cum, cumulative.

tests. The analysis revealed no significant differences in PFS (P>0.05) or OS (P>0.05) across the regimens (Fig. 2), indicating that the treatment regimen did not significantly impact survival outcomes in this cohort.

In patients with advanced-stage disease, whether chemotherapy combined with RT could improve PFS and OS was analyzed. Although the differences did not reach statistical significance, a clear trend toward improved prognosis was observed in patients receiving chemoradiotherapy. Kaplan-Meier estimates of PFS and OS are presented in Fig. 3.

Prognosis. Univariate and multivariate analyses were performed to identify the prognostic factors influencing OS and PFS in patients with NKTCL. The univariate analysis revealed that an age of >60 years and stage III/IV disease were adverse prognostic indicators for PFS in patients with NKTCL, whilst elevated LDH levels, stage III/IV disease and high EBV DNA levels were identified as adverse prognostic factors for OS (Table IV). Subsequent multivariate analysis demonstrated that an age of >60 years and stage III/IV disease were independent unfavorable prognostic factors for PFS, whilst elevated LDH levels and stage III/IV disease were established as independent adverse prognostic factors for OS (Table V). Given that treatment modality had been previously demonstrated to exert no significant impact on patient prognosis in both the univariate analyses and Kaplan-Meier survival assessments, analysis of chemotherapy regimens as a prognostic factor

Table V. Multivariate analysis of prognosis factors associated with survival.

	PFS			OS		
Factors	HR (95% CI)	P-value	Bonferroni-Hochberg adjusted P-value	HR (95% CI)	P-value	Bonferroni-Hochberg adjusted P-value
Sex (female vs. male)	1.399 (0.692-2.828)	0.350	-	1.194 (0.525-2.712)	0.672	-
Age (>60 vs. ≤60 years)	9.877 (1.305-74.732)	0.027[a]	0.036[a]	1.113 (0.364-3.405)	0.851	-
Stage (I/II vs. III/IV)	0.311 (0.143-0.676)	0.003[a]	0.012[a]	0.292 (0.112-0.761)	0.012[a]	0.024[a]
ECOG PS (0/1 vs. 2)	1.070 (0.266-4.312)	0.924	-	1.106 (0.284-4.315)	0.884	-
B symptoms (no vs. yes)	0.656 (0.333-1.292)	0.223	-	0.570 (0.247-1.315)	0.188	-
LDH (≤240 vs. >240 IU/l)	1.150 (0.416-3.182)	0.788	-	0.361 (0.136-0.956)	0.040[a]	0.040[a]
EBV DNA levels (<400 vs. ≥400 copies/ml)	0.654 (0.324-1.321)	0.236	-	0.420 (0.152-1.164)	0.095	-

[a]P<0.05. PFS, progression-free survival; OS, overall survival; HR, hazard ratio; LDH, lactate dehydrogenase; ECOG PS, Eastern Cooperative Oncology Group Performance Status.

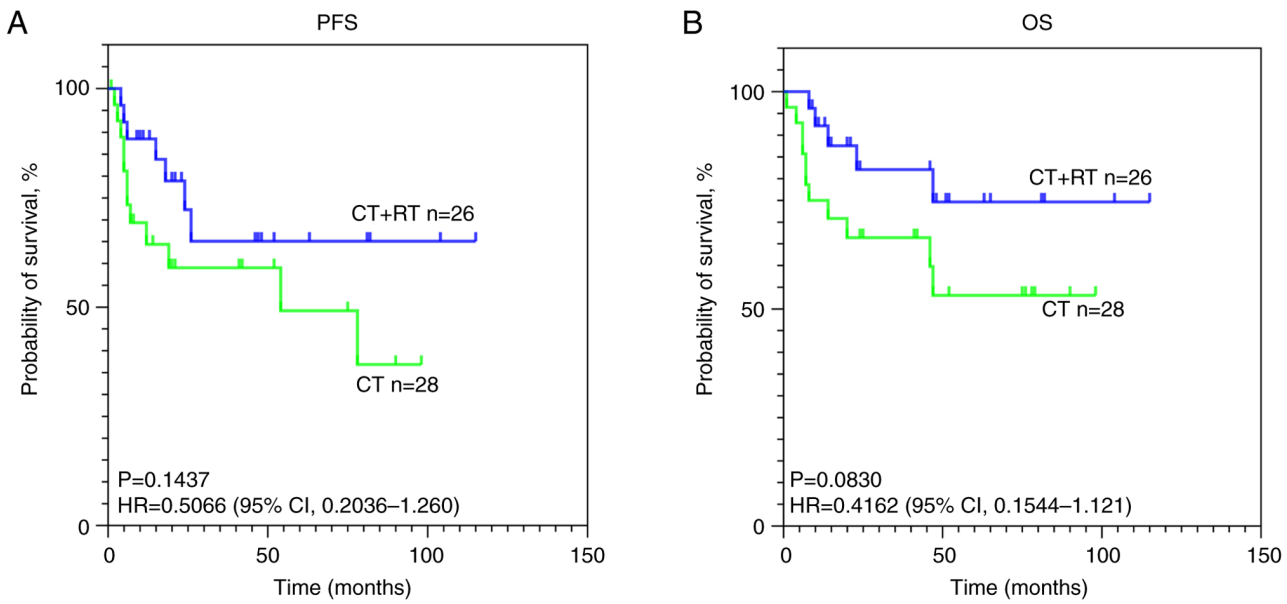

Figure 3. Kaplan-Meier survival curves of (A) PFS and (B) OS in the advanced-stage group, stratified by treatment with chemotherapy alone vs. combined chemoradiotherapy. CT, chemotherapy; RT, radiotherapy; HR, hazard ratio; PFS, progression-free survival; OS, overall survival.

was excluded from the subsequent multivariate analysis. The survival curves delineating the impact of these prognostic factors are visually presented in Fig. 4. Interaction effects among clinical variables (stage x age, stage x LDH, stage x EBV DNA and EBV DNA x age) were evaluated in multivariate Cox models. No significant interactions were observed, as shown in Fig. S1 and Table SI. The multivariate Cox models, adjusting for five covariates, yielded 7.8 (PFS) and 5.4 (OS) events per covariate, supporting reliable estimates based on the current sample size.

Discussion

NKTCL is a rare and aggressive subtype of NHL, typically characterized by a poor prognosis. The present study performed a retrospective review of a cohort comprising 171 patients with NKTCL, aiming to analyze their clinical characteristics, evaluate the efficacy of asparaginase-based treatment regimens in improving survival rates, and investigate determinants influencing the survival. The findings demonstrated that the median age of onset for NKTCL was 45 years, with a predominance of men with the disease. The etiology of NKTCL was significantly associated with EBV infection. Moreover, a preliminary assessment revealed that, except for a minority of 5 patients, all patients exhibited positive serum EBV DNA levels. Notably, the number of cases classified as early-stage exceeded those classified as late-stage.

Retrospective comparative studies have reported that asparaginase-based or pegaspargase-based regimens are

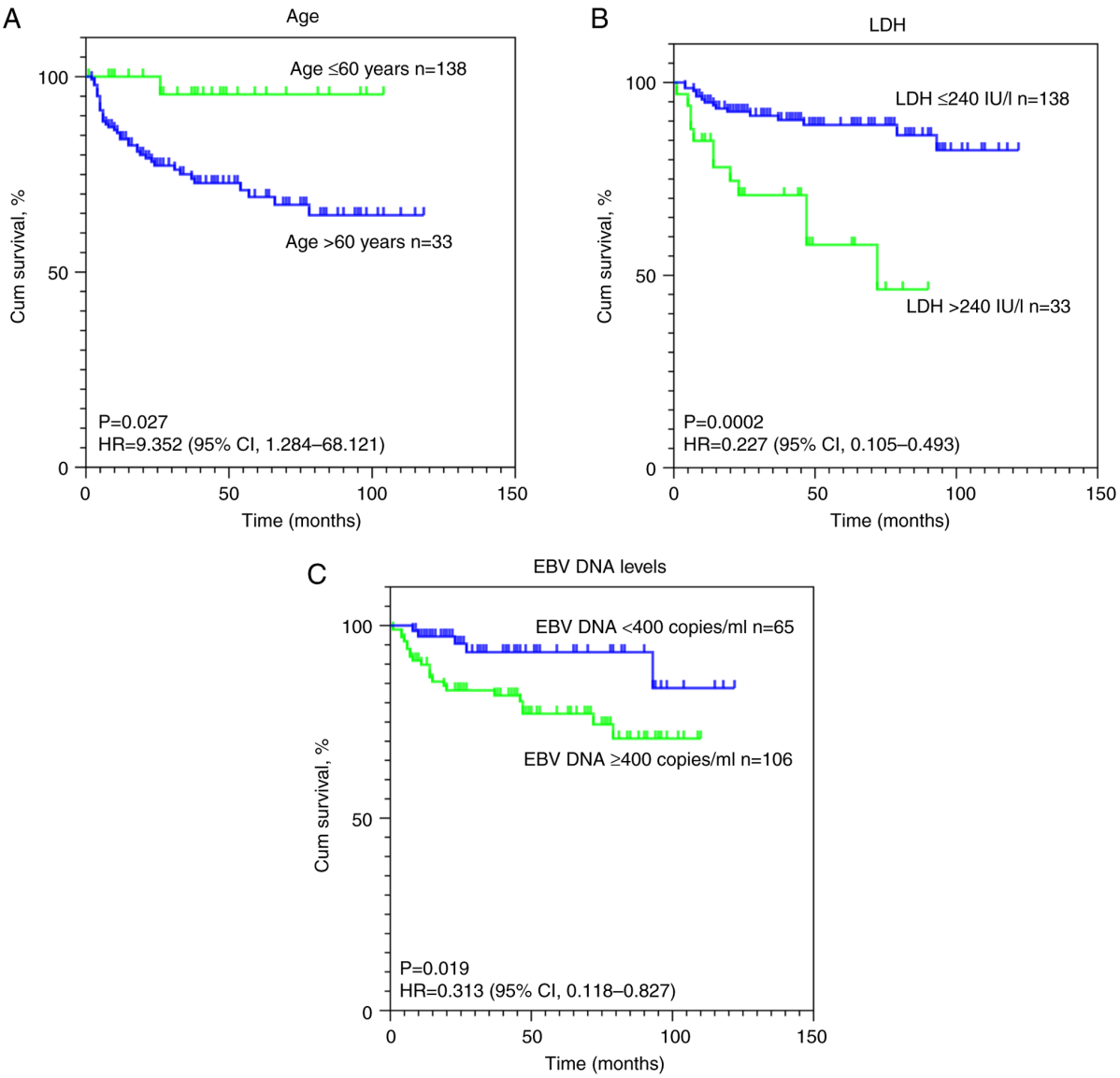

Figure 4. Multivariate Cox regression analysis of prognostic factors associated with PFS and OS. (A) PFS according to age. (B) OS stratified by LDH levels. (C) OS analysis according to EBV DNA levels. LDH, lactate dehydrogenase; EBV, Epstein-Barr virus; HR, hazard ratio; PFS, progression-free survival; OS, overall survival.

associated with superior efficacy compared with conventional anthracycline-based regimens. In a retrospective study by Wang *et al* (17), the efficacy of chemotherapy regimen GELOX (gemcitabine, l-asparaginase and oxaliplatin) was compared with those of EPOCH (etoposide, vincristine, doxorubicin, cyclophosphamide and prednisone) and CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) in the treatment of NKTCL. The results demonstrated that the 3-year OS and PFS rates in the GELOX group were significantly superior to those in the EPOCH or CHOP groups (OS, 87.0 vs. 54.0 vs. 54.0%, respectively; P<0.05; PFS, 72.0 vs. 50.0 vs. 43.0%, respectively; P<0.05). However, no significant differences in PFS (P=0.421) and OS (P=0.765) were observed between the EPOCH and CHOP groups, indicating the effectiveness of asparaginase-based chemotherapy regimens. The present study also demonstrated that asparaginase-based chemotherapy exhibited promising efficacy.

Several studies have demonstrated the value of combined RT and chemotherapy rather than chemotherapy alone in early-stage patients. The study by Cao *et al* (18) reported that sequential RT-chemotherapy combination therapy or concomitant chemo-RT (CCRT) produced a greater response than CHOP chemotherapy alone, with a CR of ~70% (RT-chemotherapy) and 77% (CCRT) compared with 60% (CHOP), and a 5-year OS rate of 42% (RT-chemotherapy) and 71% (CCRT) compared with 35% (CHOP), respectively. Huang *et al* (19) reported that in 44 patients treated with gemcitabine, cisplatin and dexamethasone, the ORR was ~95% after intensity-adjusted RT (50 Gy for primary tumor and additional 3-6 Gy for residual tumor area), with ~89% of patients achieving a CR, and the 3-year OS and PFS rates were 85 and 77%, respectively. Zhu *et al* (9) performed a study involving 30 patients who underwent concurrent chemo-RT (RT at 56 Gy/27F and chemotherapy using 25 mg/m^2 cisplatin), followed by 3 cycles of DDGP chemotherapy (dexamethasone,

cisplatin, gemcitabine and pegaspargase). The ORR was 93.3% (28/30), with all 28 patients achieving a CR at the end of treatment. The findings of the present study for early-stage patients are consistent with the results reported in the aforementioned study.

Numerous studies have also indicated that chemotherapy containing pegaspargase is superior to CHOP chemotherapy in terms of efficacy and survival rates. In a study by Bi *et al* (20), compared with the regimen without pegaspargase, the P-Gemox/GELOX regimen was associated with a significantly higher ORR in early-stage patients (92.9 vs. 51.6%; P=0.009) and demonstrated significantly improved 5-year OS rates (78.6 vs. 23.9%; P=0.010). Dong *et al* (21) reported that, compared with RT alone, the combination of L-asparaginase, cisplatin, etoposide, cyclophosphamide and dexamethasone with RT showed no significant difference in CR rates (90.9 vs. 77.8%; P=0.124). Nevertheless, the group receiving chemotherapy combined with RT exhibited higher 5-year PFS and OS rates compared with the RT-alone group (89.2 vs. 49.6%, P=0.024; and 82.9% vs. 48%, P=0.039; respectively). Huang *et al* (19) reported that the ORRs for the combination of L-asparaginase, vincristine and dexamethasone (LOP) or CHOP with RT were 89.6 and 65.6%, respectively (P=0.009), with CR rates of 68.8 vs. 50%, respectively. Furthermore, the 3-year OS and PFS rates significantly increased with LOP treatment (87.5 vs. 62.5%, P=0.006; and 79.2 vs. 50%, P=0.007; respectively), indicating the superiority of asparaginase-based chemotherapy.

The dosage of RT for NKTCL is controversial, as increasing the radiation dose may enhance efficacy, but it also increases the risk of radiation-related complications. A literature review revealed variability across different clinical centers, with doses ranging from 40-65 Gy (22,23). In the study by Wang *et al* (24), a planned prescription dose of 50 Gy was administered, with an additional 5-10 Gy of radiation dose for residual primary disease, resulting in actual doses ranging from 49.6-64 Gy, with a mean dose of 55.5 Gy. Jiang *et al* (25) utilized a dose of 56 Gy, achieving a reasonable ORR (88.5%) whilst maintaining tolerable radiation toxicity. In the study by Oh *et al* (26), which involved 62 patients diagnosed with stage I/II NKTCL, a median dose of 40 Gy of radiation therapy was administered, resulting in a total response rate of 97% and a CR rate of 90%. Among this cohort, 58 patients continued with consolidation chemotherapy, achieving 3-year OS and PFS rates of 83.1 and 77.1%, respectively. The study by Niu *et al* (27) involved 60 patients with stage I/II nasal-type extranodal NKTCL. After induction chemotherapy with pegaspargase, the patients received radiation therapy with a dose of 54.6 Gy to the tumor and positive lymph nodes, 50.7 Gy to the high-risk clinical target volume (CTV) and 45.5 Gy to the low-risk CTV, delivered in 26 fractions. The median follow-up time was 95.8 months, and the 5-year locoregional recurrence-free survival, PFS and OS rates were 83.3, 81.7 and 88.3%, respectively. In the present study, combined chemoradiotherapy with a dose of 54 Gy demonstrated favorable outcomes, with an ORR of 98.2%, a 4-year PFS rate of 82.5% (95% CI, 75.1-89.9%) and an OS rate of 92.2% (95% CI, 86.9-97.5%) for early-stage patients. For advanced-stage patients treated with pegaspargase-based chemotherapy, the 4-year PFS rate was 62.3% (95% CI, 47.4-77.2%) and the OS rate was 63.5% (95% CI, 48.2-78.8%). Both early and advanced-stage patients treated with pegaspargase-based chemotherapy demonstrated high response rates and long-term survival, consistent with the present study findings.

The EBV load is an important consideration in NKTCL. Numerous studies have reported an association between EBV viral load and prognosis. A meta-analysis performed by Liu *et al* (28) indicated that high EBV viral load before and after treatment is associated with decreased survival rates. High levels of baseline EBV DNA were significantly associated with a poor OS, with an HR of 3.45 (95% CI, 1.63-7.31; P=0.001), and a poor PFS, with an HR of 2.29 (95% CI, 1.50-3.51; P=0.0001). Similarly, patients with high EBV DNA levels post-treatment had poor PFS, with an HR of 2.36 (95% CI, 1.40-3.98; P=0.001). These findings have been corroborated by subsequent studies (29,30). Wang *et al* (31) also demonstrated that pre- and post-treatment EBV DNA positivity were associated with worse OS and PFS. Moreover, Suzuki *et al* (32) stratified patients into three prognostic groups based on post-treatment plasma EBV viral load, namely, negative, <100 copies/μg and >100 copies/μg, with significantly decreased survival rates observed in the latter two groups (P=0.001). The study by Zhong *et al* (33) also reported that the presence of EBV DNA positivity during treatment is an independent predictor of worse PFS and OS. EBV DNA positivity is associated with upregulation of chromatin remodeling changes, immune evasion-related genes and a reduction in infiltrating monocytes/M1 macrophages (34). The present study also demonstrated that EBV load is an essential factor influencing prognosis. Currently, due to the high sensitivity of quantitative-PCR and its routine applicability in several medical facilities, assessing EBV viral load in plasma samples using quantitative-PCR is crucial throughout the diagnostic, treatment and long-term follow-up phases (35). An increase in viral load levels may indicate a recurrence of lymphoma, underscoring the importance of evaluating EBV during follow-up (36).

The present study has several limitations related to its retrospective, single-center design. Reliance on incomplete or inconsistent medical records may introduce selection and information bias, potentially obscuring true treatment effects and compromising outcome assessment. Patient preference in choosing chemotherapy regimens was not controlled, which may confound survival outcomes. The single-institution setting may reflect local practices, limiting generalizability. Additionally, variable follow-up durations may affect prognostic analyses, as shorter follow-up increases censoring, while longer follow-up may overrepresent favorable outcomes. These limitations highlight the need for future prospective, multi-center studies with standardized protocols and larger, more diverse populations to validate and strengthen the findings.

In summary, NKTCL predominantly affects young men and is often associated with B symptoms. Staging is a crucial prognostic factor for both PFS and OS. Frontline therapy with pegaspargase-based chemotherapy, either alone or in combination with concurrent RT, has demonstrated promising efficacy. Future efforts should focus on optimizing treatment strategies.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

LiZ conceived the study. Data was collected, organized, validated, and managed to ensure data quality and consistency for statistical analysis by QL, XL, FZ and TL. Data collection was performed by PL, GA, LuZ, QL and XL. Data analysis was performed by PL, GA, LuZ, FZ, TL and LiZ. QL and XL were also involved in the statistical analysis. PL and GA wrote the original draft. LiZ reviewed and edited the manuscript. TL and LiZ confirm the authenticity of all the raw data. All authors contributed to the article and approved the submitted version.

Ethics approval and consent to participate

This study was conducted in accordance with the principles of the Declaration of Helsinki. The study was approved by the Ethical Review Committee of the Union Hospital, Tongji Medical College, Huazhong University of Science and Technology (Wuhan, China; approval no. 20240986). The requirement for patient approval or written informed consent to participate was waived due to the retrospective nature of the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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