Oncology and Translational Medicine
DOI 10.1007/s10330-018-0304-4
October 2018, Vol. 4, No. 5, P185–P195

ORIGINAL ARTICLE

# Analysis of clinical efficacy of P-Gemox regimen sandwich radiotherapy, P-Gemox regimen sequential radiotherapy, and radiotherapy alone treatment for extranodal natural killer/T-cell lymphoma*

**Xiaoying Quan[1], Pinjia Wang[1], Lei Lei[1], Xiaoyan Chen[1], Chunzhi Wu[1], Bin Ye[1], Zhihui Zhang[2] (✉)**

[1] Department of Medical Oncology, The Sixth People's Hospital of Chengdu, Chengdu 610051, China
[2] Department of Medical Oncology, Sichuan Cancer Hospital and Research Institute, Chengdu 610041, China

## Abstract

**Objective** The study aimed to explore the clinical efficacy of P-Gemox regimen sandwich radiotherapy, P-Gemox regimen sequential radiotherapy, and radiotherapy alone in early-stage extranodal natural killer/T-cell lymphoma (ENKTL).

**Methods** In total, 124 patients with early-stage ENKTL, from June 2009 to January 2016, were retrospectively analyzed to compare the clinical efficacy of the three regimens.

**Results** A total of 46 patients were treated with P-Gemox regimen sandwich radiotherapy, with complete remission (CR) of 91.3%, objective response rate (ORR) of 97.8%, 2-year progression-free survival (PFS) of 76.1%, and 2-year overall survival (OS) of 80.4%. Then, 37 patients received P-Gemox regimen sequential radiotherapy, with CR of 86.5%, ORR of 94.6%, 2-year PFS of 75.7%, and 2-year OS of 81.1%. Finally, 41 patients received radiotherapy alone, with CR of 61.0%, ORR of 80.5%, 2-year PFS of 51.2%, and 2-year OS of 65.9%. When the two groups were compared, significant differences in CR, PFS, and OS were observed among the sandwich radiotherapy, sequential radiotherapy, and radiotherapy alone groups ($P < 0.05$), respectively. However, no significant difference in CR, ORR, PFS, and OS was observed between the sandwich radiotherapy and sequential radiotherapy groups ($P > 0.05$). Multivariate analysis revealed that Eastern Cooperative Oncology Group (ECOG), serum lactate dehydrogenase (LDH), platelet-to-lymphocyte ratio (PLR), local tumor invasion, and treatment modalities were independent prognostic factors for PFS ($P < 0.05$). ECOG, LDH, PLR, local tumor invasion, underlying disease, and treatment modalities were independent prognostic factors for OS ($P < 0.05$).

**Conclusion** P-Gemox regimen combination radiotherapy for patients with early-stage ENKTL was better than the radiotherapy alone.

Received: 30 September 2018
Revised: 20 October 2018
Accepted: 29 October 2018

**Key words:** pegaspargase; natural killer/T-cell lymphoma; prognosis

Extranodal natural killer/T-cell lymphoma (ENKTL), nasal type, is a rare type of non-Hodgkin's lymphoma (NHL) with highly heterogeneous nasal cavity and paranasal sinus and as the primary involvement sites (approximately 80%), less commonly in non-nasal areas (approximately 20%), characterized as "lethal midline granuloma" [1]. It is more prevalent in Asia than in Western countries because of the geographic distribution [2]. Majority of patients were diagnosed as IE/IIE, and radiotherapy alone played an important role in the initial treatment. For radiotherapy alone, previous reports showed that complete remission (CR) was 70%–100%, and 5-year overall survival (OS) fluctuated from 50% to 80% [3–5]. However, the local recurrence or distant metastasis was 23%–50% [4–7]. Previous studies have confirmed that ENKTL was resistant to anthracycline-based regimens (CHOP or CHOP-like) because of high expression of P-glycoprotein (P-gp); CR was 25%–50%

✉ Correspondence to: Zhihui Zhang. Email: 13881889731@139.com
* Supported by a grant from the Scientific Research Project Foundation of Sichuan Province Health Department (No. 090528).

and 5-year OS was < 66% [8–9]. Recently, some studies demonstrated that L-asparaginase-based regimens (such as LOP, GELOX, and DIVE-L-ASP) were highly effective, with CR of up to 90.9% and 5-year OS of 64%–89.2% [10–13]. The mechanism may mainly involve the hydrolysis of the amino acid asparagine by aspariginase, blocked protein synthesis, and eventual inhibition of the proliferation of tumor cells. However, the application of L-asparaginase was limited due to its high immunogenicity. Pegaspargase was a new type of L-asparaginase with long half-life and low immunogenicity. Recently, a series of studies has shown that P-Gemox regimen is highly effective, with CR of 80%, ORR of > 90%, and 2-year OS of up to 100% [14–17]. However, due to the low incidence of this disease, previous researches were based on small sample retrospective studies. At present, no consensus has been reached on the treatment for patients with early-stage ENKTL.

The International Prognostic Index (IPI) and Korean Prognostic Index (KPI) were established on patients treated with anthracydine-based regimens, and its prognostic value remained controversial in patients with ENKTL because of imbalanced distribution [18–19]. Recently, Kim *et al* [20] established a new Prognostic Index of NK/T-cell lymphoma (PINK) model that has been proven to be effective in patients with ENKTL treated with asparaginase-based regimens. However, these prognostic models were mainly based on clinical characteristics, which could not comprehensively reflect the biology of ENKTL due to highly heterogeneous behaviors. Therefore, a simple prognostic marker is urgently needed. A previous study has shown the close association between inflammation and cancers [21]. Several studies had indicated that pretreatment platelet-to-lymphocyte ratio (PLR) was associated with poor survival in many solid cancers, including ENKTL [22–24]. However, few studies have investigated the association between PLR and patients with ENKTL treated with asparaginase-based regimens. Therefore, this study aimed to compare the efficacy of P-Gemox regimen sandwich radiotherapy, P-Gemox regimen sequential radiotherapy, and radiotherapy alone in the treatment of ENKTL.

## Materials and methods

### Patients

A total of 124 patients with newly diagnosed early-stage ENKTL were enrolled at Sichuan Province Cancer Hospital, China, from June 2009 to January 2016, according to the 2008 World Health Organization criteria [25] and clinical stage based on Ann Arbor staging [26]. These patients were included according to the following criteria: (a) pathologically and immunohistochemically confirmed diagnosis of ENKTL; (b) not under other antitumor treatment; (c) treated with P-Gemox regimen; (d) with stage III/IV, relapsed, refractory, infection, or second malignancies; and (e) with available follow-up data.

The following pretreatment information were collected: age, gender, physical examinations, B symptoms, serum lactate dehydrogenase (LDH), Ann Arbor stage, bone marrow examination, Eastern Cooperative Oncology Group (ECOG), and underlying diseases (e.g., hypertension, diabetes, hyperlipidemia). Computed tomography (CT) and/or magnetic resonance imaging (MRI) of the head and neck, chest, abdomen, and pelvis were performed. According to Ann Arbor staging, lesions localized or extending to adjacent tissues with no lymph-node involvement were defined as stage IE. PLR was defined as pretreatment platelet absolute amount to lymphocyte absolute amount ratio, with the cut-off value of 185 according to a previous study [24]. Absolute platelet and lymphocyte counts were determined using Mindray BC5800.

### Treatments

Chemotherapeutic drugs used were as follows: peg-asparaginase 2500 IU/m$^2$ intramuscular injection d1; gemcitabine 1000 mg/m$^2$ intravenous drip d1 and 8; and oxaliplatin 130 mg/m$^2$ intravenous drip d1. Radiotherapy for the involved field was delivered using 6-MeV linear accelerator, intensity-modulated radiotherapy (IMRT), giving with gross tumor volume (GTV) range of 50–60 (median dose 56) Gy and 1.8–2.0 Gy once a day, 5 days per week. P-Gemox regimen sandwich radiotherapy was defined as 2–3 cycles of chemotherapy followed by radiotherapy. P-Gemox regimen sequential radiotherapy was defined as 2–3 cycles of chemotherapy followed by radiotherapy, then continued following the original two to three cycles of chemotherapy. The treatment response according to the response criteria of NHL [27], including the CR, PR, SD, and PD.

### Follow-up

The overall survival (OS) was measured from the time of diagnosis to death due to any cause or the last follow-up visit. Progression-free survival (PFS) was defined as the time of diagnosis to the time of first disease progression, relapse, death from any cause, or the last follow-up visit.

### Statistical analysis

All data were analyzed using SPSS Statistics 17.0 (SPSS Inc., Chicago, IL). The chi-square test was used to compare the difference between the groups. Survival analysis was performed using the Kaplan-Meier curve, and differences were compared using the Log-rank test. Multivariate analysis was investigated using the Cox proportional hazard model. A two-sided $P$ value of < 0.05

was considered statistically significant.

## Results

### Patient characteristics

The baseline characteristics of 124 patients [86 men, 38 women, ratio 2.26:1, median age of 46 years (range 15–86)] are shown in Table 1. A total of 25 patients (20.2%) were older than 60 years, and 73 patients (58.9%) exhibited stage IE. Serum LDH level was elevated in 40 patients (32.3%). A total of 76 patients (61.3%) presented B symptoms. The majority of patients (75%) showed good ECOG PS score of 0–1, 62 (50%) presented local tumor invasion, and 69.4% were classified into the IPI score of 0–1. About 62.1% of patients were considered to have a KPI score of 0–1. Most of the patients (79%) were divided into the PINK score of 0, and 32 patients (25.8%) presented HB of < 120 g/L. The absolute lymphocyte count (ALC) of $< 1 \times 10^9$ /L was found 33.1% of patients. A total of 25 (20.2%) had underlying diseases, 79 (63.7%) were assigned to the low group (PLR of < 185), and the remaining 45 (36.3%) into the high group (PLR ≥ 185).

**Table 1** The baseline characteristics

| Clinical characteristics | No. of patients ($n$ = 124) | Proportion (%) |
|---|---|---|
| Age (year) | | |
| ≤ 60 | 99 | 79.8 |
| > 60 | 25 | 20.2 |
| Gender | | |
| Male | 86 | 69.4 |
| Female | 38 | 30.6 |
| ECOG | | |
| 0–1 | 93 | 75.0 |
| ≥ 2 | 31 | 25.0 |
| B symptoms | | |
| No | 48 | 38.7 |
| Yes | 76 | 61.3 |
| LDH (U/L) | | |
| ≤ 240 | 84 | 67.7 |
| > 240 | 40 | 32.3 |
| Ann Arbor stage | | |
| I E | 73 | 58.9 |
| II E | 51 | 41.1 |
| IPI score | | |
| 0–1 | 86 | 69.4 |
| ≥ 2 | 38 | 30.6 |
| KPI score | | |
| 0–1 | 77 | 62.1 |
| ≥ 2 | 47 | 37.9 |
| PINK score | | |
| 0 | 98 | 79.0 |
| ≥ 1 | 26 | 21.0 |
| Local tumor invasion | | |
| No | 62 | 50.0 |
| Yes | 62 | 50.0 |
| Pretreatment HB (g/L) | | |
| < 120 | 32 | 25.8 |
| ≥ 120 | 92 | 74.2 |
| Pretreatment ALC (/L) | | |
| $< 1 \times 10^9$ | 41 | 33.1 |
| $\geq 1 \times 10^9$ | 83 | 66.9 |
| Pretreatment PLR | | |
| < 185 | 79 | 63.7 |
| ≥ 185 | 45 | 36.3 |
| Underlying disease | | |
| No | 99 | 79.8 |
| Yes | 25 | 20.2 |
| Treatment modalities | | |
| Radiotherapy alone | 41 | 33.1 |
| P-Gemox sequential radiotherapy | 37 | 29.8 |
| P-Gemox sandwich radiotherapy | 46 | 37.1 |

### Treatment response

The treatment responses are shown in Table 2. In all patients, CR was 79.8%, PR was 11.3%, and ORR was 91.1%. A total of 46 patients were treated with P-Gemox regimen sandwich radiotherapy, with CR of 91.3%, PR of 6.5%, and ORR of 97.8%. Then, 37 patients received P-Gemox regimen sequential radiotherapy, with CR of 86.5%, PR of 8.1%, and ORR of 94.6%. Finally, 41 patients received radiotherapy alone, with CR of 61.0%, PR of 19.5%, and ORR of 80.5%. No significant differences in the CR ($P$ = 0.001) and ORR ($P$ = 0.012) were observed among the three groups. Further two-group comparison analysis, significant differences in the CR ($P$ = 0.001) and ORR ($P$ = 0.022) were observed between the sandwich radiotherapy and radiotherapy alone. Meanwhile, significant difference in the CR ($P$ = 0.011) was observed between the sequential radiotherapy and radiotherapy alone. On the contrary, no significant difference in the ORR ($P$ = 0.128) was observed between the sequential radiotherapy and radiotherapy alone. In addition, no significant difference in the CR ($P$ = 0.729) and ORR ($P$ = 0.847) was observed between the sandwich radiotherapy and sequential radiotherapy.

### Adverse reactions to chemotherapy

The main adverse reactions to chemotherapy are summarized in Table 3. Grade 1/2 were commonly observed, and Grade 3/4 occurred less frequently. Compared with the sequential radiotherapy, sandwich radiotherapy was more likely to cause Grade 1/2 elevated transaminase ($P$ = 0.037), but no significant difference was found in other adverse reactions. No serious infection or hemorrhage occurred. No treatment-related death was noted.

**Table 2** The treatment responses [*n* (%)]

| Treatment response | Radiotherapy alone | P-Gemox sequential radiotherapy | P-Gemox sandwich radiotherapy | $\chi^2$ | *P* |
|---|---|---|---|---|---|
| CR | 25 (61.0) | 32 (86.5) | 42 (91.3) | 13.836 | 0.001 |
| PR | 8 (19.5) | 3 (8.1) | 3 (6.5) | 4.186 | 0.123 |
| ORR | 33 (80.5) | 35 (94.6) | 45 (97.8) | 8.845 | 0.012 |

**Table 3** The chemotherapy adverse reactions [*n* (%)]

| Chemotherapy side effects | P-Gemox sequential radiotherapy | P-Gemox sandwich radiotherapy | $\chi^2$ | *P* |
|---|---|---|---|---|
| Leukopenia | | | | |
| I–II | 19 (51.4) | 18 (39.1) | 1.240 | 0.266 |
| III–IV | 16 (43.2) | 27 (58.7) | 1.961 | 0.161 |
| Anemia | | | | |
| I–II | 20 (54.1) | 28 (60.9) | 0.391 | 0.532 |
| III–IV | 10 (27.0) | 10 (21.7) | 0.313 | 0.576 |
| Thrombocytopenia | | | | |
| I–II | 17 (45.9) | 20 (43.5) | 0.051 | 0.822 |
| III–IV | 11 (29.7) | 16 (34.8) | 0.239 | 0.625 |
| Gastrointestinal reaction | | | | |
| I–II | 12 (32.4) | 18 (39.1) | 0.399 | 0.528 |
| III–IV | 6 (16.2) | 8 (17.4) | 0.020 | 0.887 |
| Elevated transaminases | | | | |
| I–II | 14 (37.8) | 28 (60.9) | 4.352 | 0.037 |
| III–IV | 4 (10.8) | 4 (8.7) | 0 | 1 |
| Hyperbilirubinemia | | | | |
| I–II | 19 (51.4) | 22 (47.8) | 0.102 | 0.750 |
| III–IV | 1 (2.7) | 0 (0) | 0.012 | 0.913 |
| Hypoproteinemia (g/L) | | | | |
| 28 ≤ ALB < 35 | 20 (54.1) | 23 (50.0) | 0.135 | 0.713 |
| ALB < 28 | 7 (18.9) | 7 (15.2) | 0.200 | 0.654 |

## Prognostic factor analysis

The results of prognostic factor analysis for PFS are displayed in Table 4. Univariate analysis showed the following results: ECOG score (≥ 2), B symptoms, LDH of ≥ 240 U/L, IPI score (≥ 2), KPI score (≥ 2), ALC of $< 1 \times 10^9$ /L, PLR of ≥ 185, GTV of ≤ 55 Gy, local tumor invasion, and treatment modalities, which were significantly associated with poor PFS (all $P < 0.05$). Multivariate analysis showed that ECOG, LDH, PLR, local tumor invasion, and treatment modalities were independent prognostic factors for PFS.

The results of prognostic factor analysis for OS are shown in Table 4. Univariate analysis showed that age (> 60 years), ECOG score (≥ 2), B symptoms, LDH of ≥ 240 U/L, IPI score (≥ 2), KPI score (≥ 2), PINK score (≥ 1), ALC of $< 1 \times 10^9$ /L, PLR of ≥ 185, GTV of ≤ 55 Gy, local tumor invasion, underlying diseases, and treatment modalities were significantly correlated with poorer OS (all $P < 0.05$). Multivariate analysis demonstrated that ECOG, LDH, PLR, local tumor invasion, underlying diseases, and treatment modalities were independent prognostic factors for OS.

## Survival analysis

Among the 124 patients, 49 died, whereas 75 patients survived as of March 2018. The overall median survival was 32 (range 3–103) months, 2-year PFS was 67.7% (Fig. 1a), and 2-year OS was 75.8% for all patients (Fig. 1b).

The 2-year PFS in P-Gemox regimen sandwich radiotherapy, P-Gemox regimen sequential radiotherapy, and radiotherapy alone were 76.1%, 75.7%, and 51.2%, respectively, which were significantly different among the three groups (Fig. 2a). In the further two-group comparison analysis, no significant difference was observed between sandwich radiotherapy and sequential radiotherapy (Fig. 2b). Significant differences were observed between radiotherapy alone and sandwich radiotherapy, and sequential radiotherapy (Fig. 2c and 2d).

In addition, the 2-year OS for P-Gemox regimen sandwich radiotherapy, P-Gemox regimen sequential radiotherapy, and radiotherapy alone were 80.4%, 81.1%, and 65.9%, respectively, with no significant differences (Fig. 3a). In the further two-group analysis, no significant

**Table 4** The prognostic factor analysis for progression free survival and overall survival

| Clinical characteristics | | PFS | | | | OS | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Univariate analysis (*P*) | Multivariate analysis | | | Univariate analysis (*P*) | Multivariate analysis | | |
| | | | HR | 95% CI | *P* | | HR | 95% CI | *P* |
| Age (year) | ≤ 60 | 0.137 | | | | 0.034 | 1355.099 | 0–2.067E$^{80}$ | 0.937 |
| | > 60 | | | | | | | | |
| Gender | Male | 0.716 | | | | 0.508 | | | |
| | Female | | | | | | | | |
| ECOG | 0–1 | < 0.001 | 6.023 | 2.165–16.757 | 0.001 | < 0.001 | 4.279 | 1.600–11.442 | 0.004 |
| | ≥ 2 | | | | | | | | |
| B symptoms | No | 0.037 | 1.264 | 0.567–2.818 | 0.566 | 0.029 | 1.591 | 0.683–3.708 | 0.282 |
| | Yes | | | | | | | | |
| LDH (U/L) | ≤ 240 | < 0.001 | 2.703 | 1.342–5.443 | 0.005 | < 0.001 | 2.509 | 1.159–5.432 | 0.020 |
| | > 240 | | | | | | | | |
| Ann Arbor stage | I | 0.056 | | | | 0.052 | | | |
| | II | | | | | | | | |
| IPI score | 0–1 | 0.001 | 0.377 | 0.137–1.039 | 0.059 | < 0.001 | 0.788 | 0.261–2.373 | 0.671 |
| | ≥ 2 | | | | | | | | |
| KPI score | 0–1 | 0.035 | 0.867 | 0.375–2.005 | 0.739 | 0.021 | 0.735 | 0.304–1.780 | 0.495 |
| | ≥ 2 | | | | | | | | |
| PINK score | 0 | 0.192 | | | | 0.049 | 0 | 0–6.044E$^{73}$ | 0.931 |
| | ≥ 1 | | | | | | | | |
| Local tumor invasion | No | 0.033 | 2.292 | 1.080–4.862 | 0.031 | 0.022 | 2.308 | 1.031–5.164 | 0.042 |
| | Yes | | | | | | | | |
| Pretreatment HB (g/L) | < 120 | 0.298 | | | | 0.167 | | | |
| | ≥ 120 | | | | | | | | |
| Pretreatment ALC (/L) | < 1 × 10$^9$ | 0.034 | 0.792 | 0.390–1.610 | 0.519 | 0.030 | 0.981 | 0.482–1.998 | 0.985 |
| | ≥ 1 × 10$^9$ | | | | | | | | |
| Pretreatment PLR | < 185 | < 0.001 | 2.876 | 1.414–5.850 | 0.004 | 0.001 | 2.913 | 1.358–6.250 | 0.006 |
| | ≥ 185 | | | | | | | | |
| GTV (Gy) | 50–55 | 0.020 | 0.982 | 0.522–1.850 | 0.956 | 0.013 | 0.712 | 0.368–1.378 | 0.314 |
| | 56–60 | | | | | | | | |
| Underlying disease | No | 0.073 | | | | 0.028 | 2.752 | 1.339–5.654 | 0.006 |
| | Yes | | | | | | | | |
| Treatment modalities | Radiotherapy alone | 0.015 | 1.811 | 1.201–2.732 | 0.005 | 0.009 | 2.001 | 1.270–3.150 | 0.003 |
| | P-Gemox sequential radiotherapy | | | | | | | | |
| | P-Gemox sandwich radiotherapy | | | | | | | | |

difference was observed between sandwich radiotherapy and sequential radiotherapy (Fig. 3b), whereas significant differences were observed between radiotherapy alone and sandwich radiotherapy and sequential radiotherapy (Fig. 3c and 3d).

### Prognostic values of combining PLR with IPI, KPI, and PINK

In our study, 69.4% of cases were grouped into IPI score (0–1), which failed to distinguish between patients with different outcomes. When we combined PLR with IPI scores (0–1), which was found to distinguish survival difference of the low-risk group (Fig. 4a and 4b). Besides, 62.1% of cases were divided into KPI score (0–1), which could not distinguish the survival difference. When we combined PLR with KPI score, which could identify the survival difference in the low-intermediate risk group (Fig. 4c and 4d). In addition, 79% of cases were assigned into PINK score (0), which was also unsatisfactory to significantly identify the survival difference. The PLR combined with the PINK score could distinguish survival difference in the low-risk group (Fig. 4e and 4f).

## Discussion

ENKTL was a heterogeneous disease with highly invasive biological behavior, and the clinical efficacy and survival showed individual difference. Radiotherapy was the main treatment strategy for patients with early-stage ENKTL who achieved better treatment response, but local recurrence or distant metastasis was close to 50% [3–7]. Radiation dose was found to be one

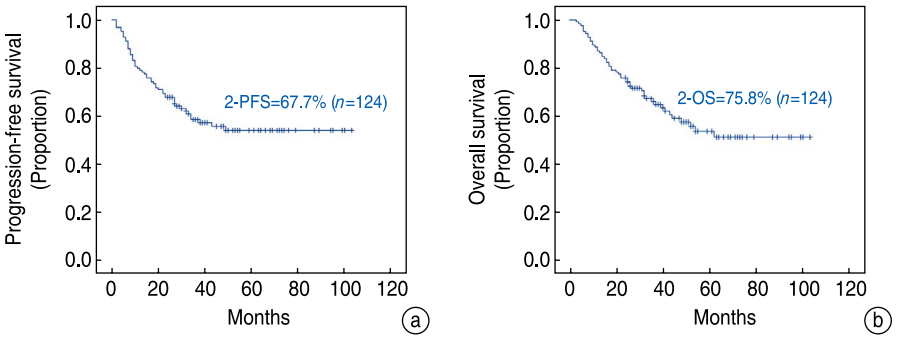


**Fig. 1** The survival curve of the whole patients. (a) Progression free survival for whole patients; (b) Overall survival for whole patients

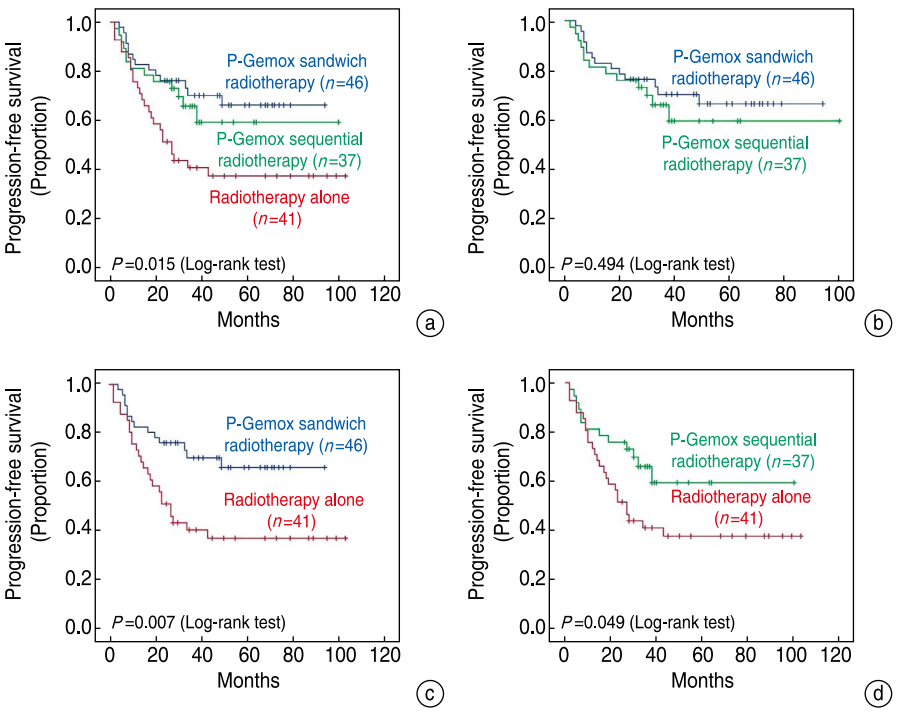


**Fig. 2** The different treatment modalities for progression free survival. (a) The difference of P-Gemox sandwich radiotherapy, P-Gemox sequential radiotherapy, and radiotherapy alone; (b) The difference of P-Gemox sandwich radiotherapy and P-Gemox sequential radiotherapy; (c) The difference of P-Gemox sandwich radiotherapy and radiotherapy alone; (d) The difference of P-Gemox sequential radiotherapy and radiotherapy alone

of the factors that affected the therapeutic effect. A multicenter retrospective study [28] proposed the dose-effect relationship, suggesting that no less than 50 Gy dose can obtain higher local regional control and long-term survival. Similarly, Yang *et al* conducted a study [29] that also reported satisfactory results, with CR of 78.4%, ORR of 91.2%, 3-year PFS and OS of 64.0% and 76.3%, respectively. In our study, all patients received intensity-modulated radiation therapy with no less than 50 Gy and radiotherapy alone with CR of 61%, ORR of 80.5%, and 2-year PFS and OS of 51.2%, 65.9%, respectively, which is consistent with previous studies [28–29]. Based on the further analysis on radiation doses, the high-dose group (56–60 Gy) was better than the low-dose group (50–55 Gy). Significant differences in the CR, PFS, and OS were observed between the two groups, suggesting that the relative high dose could improve prognosis [6–7]. However, no statistically significant difference was observed for ORR. This may be because of radiotherapy's key role in patients with early-stage ENKTL, and our study also showed the advantage of radiotherapy of no less than 50 Gy.

Previous studies confirmed that ENKTL was not sensitive to anthracycline-based regimens because of

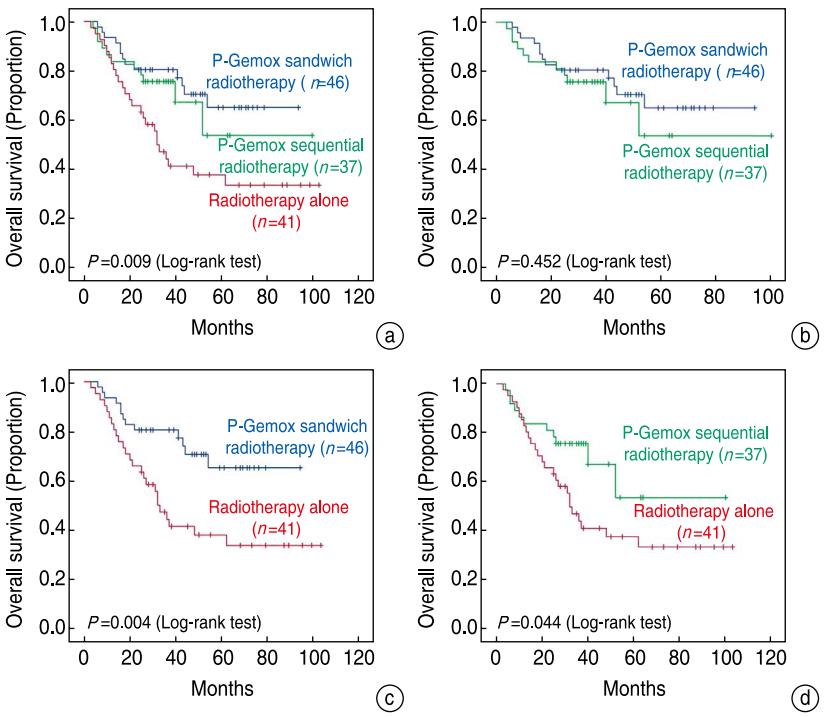


**Fig. 3** The different treatment modalities for overall survival. (a) The difference of P-Gemox sandwich radiotherapy, P-Gemox sequential radiotherapy, and radiotherapy alone; (b) The difference of P-Gemox sandwich radiotherapy and P-Gemox sequential radiotherapy; (c) The difference of P-Gemox sandwich radiotherapy and radiotherapy alone; (d) The difference of P-Gemox sequential radiotherapy and radiotherapy alone

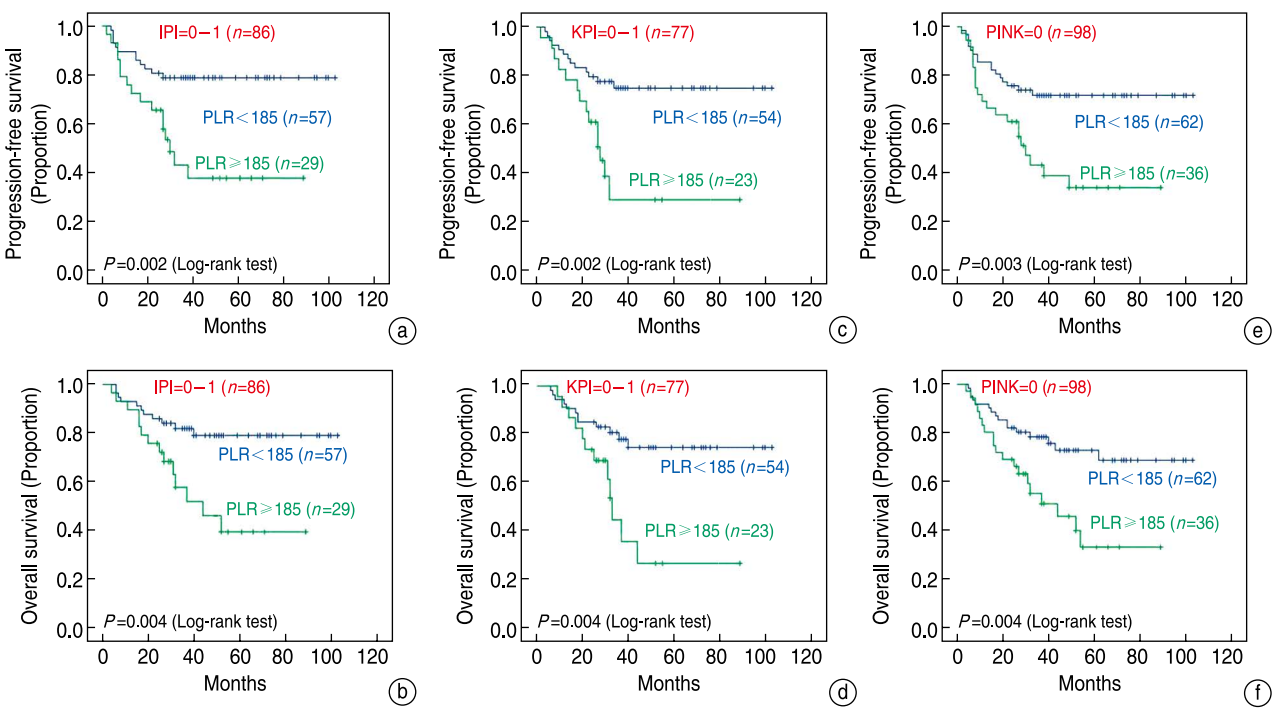


**Fig. 4** The relationships between PLR and IPI, KPI, PINK score. (a) Combing PLR and IPI score 0–1 for PFS; (b) Combing PLR and IPI score 0–1 for OS; (c) New model combing PLR and KPI score 0–1 for PFS; (d) New model combing PLR and KPI score 0–1 for OS; (e) Combing PLR and PINK score 0 for PFS; (f) Combing PLR and PINK score 0 for OS

P-glycoprotein expression [8–9]. Recently studies showed that L-asparaginase-based regimens improved clinical efficacy [10–13]. However, due to L-asparaginase with high immunogenicity, allergic reaction is increasing. Pegaspargase showed lower immunogenicity. Recently researches reported P-Gemox regimen in the treatment of patients with early-stage ENKTL showed satisfactory results, with CR of up to 80%, ORR of 90%, 2-year PFS of approximately 87%, 2-year OS of nearly 100% [14–17]. In this study, P-Gemox regimen sequential radiotherapy and P-Gemox regimen sandwich radiotherapy achieved significant results, with CR of 86.5%, 91.3%, ORR of 94.6%, 97.8%, 2-year PFS of 75.7%, 76.1%, 2-year OS of 81.1%, 80.4%, respectively. It suggested that P-Gemox regimen remarkably improved prognosis, which is similar to the findings of previous studies [14–17]. Further survival curve analysis showed that P-Gemox regimen sandwich radiotherapy was slightly superior than P-Gemox regimen sequential radiotherapy, but the difference was not significant. The reasons are as follows: (1) all the cases included were early-stage patients; (2) small retrospective study, and shorter follow-up time; and (3) highly heterogeneous disease. Based on the existing studies, whether the difference between the two groups could not be known, the next step should be to prolong the follow-up time and increase the sample size.

The IPI score was used to estimate the prognosis of NHL, but limited to ENKTL patients, because most patients were classified as low-risk group [18]. The KPI score showed good prospects than IPI score in the distribution, but KPI score cannot further distinguish between the differences in early stage patients [19]. Meanwhile, these prognostic models were mainly based on anthracycline regimen, which were limited in non-anthracycline regimen. Recently, PINK score [20] based on non-anthracycline chemotherapy showed good advantages. However, these models were all mainly based on the clinical features and not completely reflect the biological characteristics of ENKTL. Therefore, a simple comprehensive prognostic marker is needed.

Leukocytes, neutrophils, and monocytes in the peripheral blood could reflect the inflammation, and lymphocytes reflected the immunity. Both inflammatory and immune responses were important factors of tumor microenvironment. One study showed that inflammatory response was closely related to the development of tumors [21]. Lymphocyte was one of the important immune defense factors and immune surveillance and inhibit the proliferation of tumor cells. The decreasing lymphocyte levels can lead to immunosuppression, decreasing the ability of the host's immune function. A study [30] reported that some immunosuppressive factors involved the inflammatory response process, such as interleukin-10 (IL-10) and transforming growth factor-β (TGF-β), with the mechanism that may be mediated by cytotoxic T cells destroying lymphocyte. Therefore, the study showed that lymphocyte reduction was an independent prognostic factor for ENKTL [31].

Cancer patients are often accompanied with high coagulation state because of secondary thrombocytosis. Some studies [32–33] found the release of pro-inflammatory cytokines (IL-10, IL-6, etc.) in the microenvironment stimulated the production of megakaryocytes, causing the proliferation of platelets. Its mechanism may be that increasing platelets may inhibit the antitumor ability of natural killer cells, evading immune surveillance, leading to proliferation and migration of tumor cells. Based on the above results, thrombocytosis may be related to the prognosis of tumors. Therefore, PLR was a simply feasible prognostic marker, consisting of platelets and lymphocytes, and has been proven to of prognostic value in multiple solid tumors [22–23]. However, studies on the relationship between PLR and ENKTL treated with P-Gemox regimen were limited. Wang *et al* [24] conducted a retrospective study on 252 patients with early-stage ENKTL with the following results: based on the ROC curve cut-off value for PLR of 185, significant difference was observed between the low (PLR of < 185) and high groups (PLR of >185) for the 5-year OS (72.3% vs 53.9%). Thus, PLR was considered as an independent prognostic factor. In the present study, significant differences were also observed between the two groups (2-PFS 74.7% vs 55.6%; 2-OS 81.0% vs 66.7%). Therefore, this study [24] concluded that PLR was an independent prognostic factor.

Based on the IPI, KPI, and PINK scores [18–20], most patients were classified as low-risk group because of imbalanced distribution. Therefore, in order to further verify the prognostic value of PLR, a new model was established. When PLR was combined with IPI score of 0–1, KPI score of 0–1, and PINK score of 0, the survival differences were observed among the low-risk groups (Fig. 4). Therefore, PLR may be more accurate to balance the distribution than the IPI, KPI, and PINK. This may be because peripheral blood indicators (white blood cell, neutrophil, lymphocyte, platelet, etc.) were important parts of the tumor microenvironment, and those anomaly inflammatory markers were already present prior to the occurrence of other clinical signs. Therefore, PLR was a new marker to predetermine the prognosis. The value of PLR was further verified by multicenter large-sample randomized controlled trials.

Anemia was often observed in malignant tumors. Previous studies reported that anemia was a prognostic indicator of follicular lymphoma [34]. The main mechanism was that anemia increased the number of hypoxic cells, leading to treatment resistance. However, another study

showed that anemia was not a prognostic factor for ENKT [35]. Meanwhile, anemia was not correlated with prognosis in our study, which was consistent with that of the previous study [35]. This may be because the patients included had early-stage disease, and the sample size was small. Moreover, most studies confirmed that age was an independent prognostic factor [24, 31, 35]. However, one study demonstrated the opposite conclusion [36]. Our study showed that age was related to OS, but was not independent prognostic factor. The reasons are as follows: (1) imbalance distribution, only 20.2% of patients aged 60 years; (2) compared with anthracycline-based regimens, P-Gemox showed high efficacy, low toxicity, and was tolerable by elderly patients; and (3) existing medical technology help the elderly to tolerate chemotherapy and radiotherapy. Therefore, it optimized the chemotherapy regimen. However, with the improvement of accurate radiotherapy, decreasing age effect the prognosis. Whether age continued to be a prognostic factor for this disease remains to be further verified. In addition, LDH, clinical stage, and local tumor invasion may reflect the tumor load. Consistent with previous studies [24, 35, 37], our study found that LDH, ECOG, and local tumor invasion were independent prognostic factors. However, the stage was not an independent prognostic factor because of the following reasons: (1) not extensively performed sensitive technologies such as PET/CT caused low detection rate of the neck lymph node, which can lead to not entirely accurate stage and (2) early-stage patients were sensitive to radiotherapy with good prognosis. In addition, B symptoms were correlated with poor survival, but not as an independent factor, in this study [24]. This may be because of the short follow-up time and small sample of this retrospective study. A previous study have reported that the lymphocyte was an independent prognostic indicator [31]. Our study found that it was not an independent prognostic factor, because PLR was also included in the multivariate analysis, and better prognostic value than lymphocyte.

Several studies have showed the relationship between underlying diseases and cancers. One study [38] has found that hyperlipidemia was a risk factor for NHL. Another study [39] confirmed that low level high-density lipoprotein was a poor prognostic factor for ENKTL. Because abnormal lipids can increase free radicals and damage DNA. Some reports [40–41] showed that diabetes was associated with tumor formation; the mechanism may involve the activation of insulin-like growth factor that causes abnormal growth hormone secretion and promotes the growth of tumor. In addition, some studies [42–43] found that hypertension also was one of the risk factors of the occurrence of tumor, which may be the condition of heavy load, damaged the vessel wall, released a series of inflammatory factors, and suppressed the immune system. In this study, underlying diseases (hyperlipidemia, diabetes, hypertension, etc.) were independent prognostic factors for OS. This may be because patients with underlying diseases were not satisfactory with treatment. The specific mechanism was worth further discussion. Therefore, individualized treatment is very important.

Another concerning issue was chemotherapeutic side effects. A study from Japan [44] reported that 100% of patients had Grade 3/4 neutropenia and 32% had abnormal liver function in the SMILE regimen. Another study from France [45] showed that 42% of patients had Grade 3/4 neutropenia and 16% had Grade 3/4 abnormal liver function in the AspaMetDex regimen. Compared with the above regimens, P-Gemox regimen was relatively mild and safe, with 51.8% of patients having Grade 3/4 leukopenia, 24.1% having Grade 3/4 anemia, 32.5% having Grade 3/4 thrombocytopenia, Grade 3/4 elevated transaminase only 9.6%, and Grade 3/4 hyperbilirubinemia in only one patient (1.2%), with no coagulation disorder. Further analysis comparing the P-Gemox regimen sequential radiotherapy with P-Gemox regimen sandwich radiotherapy showed that the latter was more likely to cause Grade1/2 increased transaminases ($P < 0.05$), because of increasing chemotherapy cycles. Notably, hypoproteinemia occurred as a side effect because of (l) nausea and vomiting that resulted in insufficient intake and (2) radiation mucositis and pain affected intake. Therefore, nutritional support should be strengthened to improve patients' general condition.

## Conclusion

P-Gemox combination radiotherapy as the first-line treatment for ENKTL was found to be highly effective and was better than radiotherapy alone. The difference between P-Gemox regimen sandwich radiotherapy and P-Gemox regimen sequential radiotherapy should be assessed in large-sample randomized controlled trials in the future.

## Conflicts of interest

The authors indicated no potential conflicts of interest.

# References

1. Tse E, Kwong YL. How I treat NK/T-cell lymphomas. Blood, 2013, 121: 4997–5005.
2. Liao Y, Du XB, Zou QF, Extranodal natural killer/T-cell lymphoma, nasal type: epidemiology study. Chinese-German J Clin Oncol, 2012, 11: 290–293.
3. Tse E, Kwong YL. Nasal NK/T-cell lymphoma: RT, CT, or both. Blood, 2015, 126: 1400–1401.
4. Li YX, Liu QF, Wang WH, *et al*. Failure patterns and clinical implications in early stage nasal natural killer/T-cell lymphoma treated with primary radiotherapy. Cancer, 2011, 117: 5203–5211.

5. Li YX, Wang H, Jin J, *et al*. Radiotherapy alone with curative intent in patients with stage I extranodal nasal-type NK/T-cell lymphoma. Int J Radiat Oncol Biol Phys, 2012, 82: 1809–1815.
6. Bi XW, Li YX, Fang H, *et al*. High-dose and extended-field intensity modulated radiation therapy for early-stage NK/T-cell lymphoma of Waldeyer's ring: dosimetric analysis and clinical outcome. Int J Radiat Oncol Biol Phys, 2013, 87: 1086–1093.
7. Wang H, Li YX, Wang WH, *et al*. Mild toxicity and favorable prognosis of high-dose and extended involved-field intensity-modulated radiotherapy for patients with early-stage nasal NK/T-cell lymphoma. Int J Radiat Oncol Biol Phys, 2012, 82: 1115–1121.
8. Huang H, Lin Z, Lin X, *et al*. Long-term outcomes of patients with newly diagnosed extranodal natural killer/T-cell lymphoma treated by etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin regimen: a single-institution experience. Leuk Lymphoma, 2011, 52: 1041–1048.
9. Wang L, Xia ZJ, Huang HQ, *et al*. Cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) in the treatment of stage IE/IIE extranodal natural killer/T cell lymphoma, nasal type: 13-year follow-up in 135 patients. Int J Hematol, 2012, 96: 617–623.
10. Jiang M, Zhang H, Jiang Y, *et al*. Phase 2 trial of "sandwich" L-asparaginase, vincristine, and prednisone chemotherapy with radiotherapy in newly diagnosed, stage IE to IIE, nasal type, extranodal natural killer/T-cell lymphoma. Cancer, 2012, 118: 3294–3301.
11. Zhang L, Jiang M, Xie L, *et al*. Five-year analysis from phase 2 trial of "sandwich" chemoradiotherapy in newly diagnosed, stage IE to IIE, nasal type, extranodal natural killer/T-cell lymphoma. Cancer Med, 2016, 5: 33-40.
12. 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.
13. Dong LH, Zhang LJ, Wang WJ, *et al*. Sequential DICE combined with l-asparaginase chemotherapy followed by involved field radiation in newly diagnosed, stage IE to IIE, nasal and extranodal NK/T-cell lymphoma. Leuk Lymphoma, 2016, 57: 1600–1606.
14. Liang SP, Wang HQ, Zhang HL, *et al*. Clinical efficacy of pegaspargase plus GEMOX regimen for initial treatment of nasal NK/T-cell lymphoma. Chin J Clin Oncol (Chinese), 2014, 41: 1225–1228.
15. Wang JH, Wang H, Wang YJ, *et al*. Analysis of the efficacy and safety of a combined gemcitabine, oxaliplatin and pegaspargase regimen for NK/T-cell lymphoma. Oncotarget, 2016, 7: 35412–35422.
16. Wei W, Wu P, Li L, *et al*. Effectiveness of pegaspargase, gemcitabine, and oxaliplatin (P-GEMOX) chemotherapy combined with radiotherapy in newly diagnosed, stage IE to IIE, nasal-type, extranodal natural killer/T-cell lymphoma. Hematology, 2017, 22: 320–329.
17. Jing XM, Zhang ZH, Wu P, *et al*. Efficacy and tolerance of pegaspargase, gemcitabine and oxaliplatin with sandwiched radiotherapy in the treatment of newly-diagnosed extranodal nature killer (NK)/T cell lymphoma. Leuk Res, 2016, 47: 26–31.
18. Chim CS, Ma SY, Au WY, *et al*. Primary nasal natural killer cell lymphoma: long-term treatment outcome and relationship with the International Prognostic Index. Blood, 2004, 103: 216–221.
19. 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.
20. Kim SJ, Yoon DH, Jaccard A, *et al*. A prognostic index for natural killer cell lymphoma after non-anthracycline-based treatment: a multicentre, retrospective analysis. Lancet Oncol, 2016, 17: 389–400.
21. Schreiber RD, Old LJ, Smyth MJ. Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. Science, 2011, 331: 1565–1570.
22. Krenn-Pilko S, Langsenlehner U, Thurner EM, *et al*. The elevated preoperative platelet-to-lymphocyte ratio predicts poor prognosis in breast cancer patients. Br J Cancer, 2014, 110: 2524–2530.
23. Li F, Hu H, Gu S, *et al*. Platelet to lymphocyte ratio plays an important role in prostate cancer's diagnosis and prognosis. Int J Clin Exp Med, 2015, 8: 11746–11751.
24. Wang KF, Chang BY, Chen XQ, *et al*. A prognostic model based on pretreatment platelet lymphocyte ratio for stage IE/IIE upper aerodigestive tract extranodal NK/T cell lymphoma, nasal type. Med Oncol, 2014, 31: 318.
25. Tohda S. Overview of lymphoid neoplasms in the fourth edition of the WHO classification. Rinsho Byori (Japanese), 2012, 60: 560–564.
26. Carbone PP, Kaplan HS, Musshoff K, *et al*. Report of the Committee on Hodgkin's Disease Staging Classification. Cancer Res, 1971, 31: 1860–1861.
27. Cheson BD, Pfistner B, Juweid ME, *et al*. Revised response criteria for malignant lymphoma. J Clin Oncol, 2007, 25: 579–586.
28. Yang Y, Cao JZ, Lan SM, *et al*. Association of improved locoregional control with prolonged survival in early-stage extranodal nasal-type natural killer/T-cell lymphoma. JAMA Oncol, 2017, 3: 83–91.
29. Yang CW, Wang CW, Hong RL, *et al*. Treatment outcomes of and prognostic factors for definitive radiotherapy with and without chemotherapy for Stage I/II nasal extranodal NK/T-cell lymphoma. J Radiat Res, 2017, 58: 114–122.
30. Salazar-Onfray F, López MN, Mendoza-Naranjo A. Paradoxical effects of cytokines in tumor immune surveillance and tumor immune escape. Cytokine Growth Factor Rev, 2007, 18: 171–182.
31. Huang JJ, Jiang WQ, Lin TY, *et al*. Absolute lymphocyte count is a novel prognostic indicator in extranodal natural killer/T-cell lymphoma, nasal type. Ann Oncol, 2011, 22: 149–155.
32. Labelle M, Begum S, Hynes RO. Direct signaling between platelets and cancer cells induces an epithelial-mesenchymal-like transition and promotes metastasis. Cancer Cell, 2011, 20: 576–590.
33. Buergy D, Wenz F, Groden C, *et al*. Tumor-platelet interaction in solid tumors. Int J Cancer, 2012, 130: 2747–2760.
34. Solal-Céligny P, Roy P, Colombat P, *et al*. Follicular lymphoma international prognostic index. Blood, 2004, 104: 1258–1265.
35. Li JW, Li YJ, Zhong MZ, *et al*. Efficacy and tolerance of GELOXD/P-GEMOXD in newly diagnosed nasal-type extranodal NK/T-cell lymphoma: A multicenter retrospective study. Eur J Haematol, 2018, 100: 247–256.
36. Yang Y, Zhang YJ, Zhu Y, *et al*. Prognostic nomogram for overall survival in previously untreated patients with extranodal NK/T-cell lymphoma, nasal-type: a multicenter study. Leukemia, 2015, 29: 1571–1577.
37. Kim TM, Park YH, Lee SY, *et al*. Local tumor invasiveness is more predictive of survival than International Prognostic Index in stage I(E)/II(E) extranodal NK/T-cell lymphoma, nasal type. Blood, 2005, 106: 3785–3790.
38. Lim U, Gayles T, Katki HA, *et al*. Serum high-density lipoprotein cholesterol and risk of non-Hodgkin lymphoma. Cancer Res, 2007, 67: 5569–5574.
39. Wang L, Chi PD, Chen H, *et al*. Low level of high-density lipoprotein cholesterol correlates with poor prognosis in extranodal natural killer/T cell lymphoma. Tumor Biol, 2014, 35: 2141–2149.

40. Inoue M. Diabetes, and cancer – epidemiologic evidence. Gan To Kagaku Ryoho (Japanese), 2015, 42: 521–524.
41. Shi Y, Hu FB. The global implications of diabetes and cancer. Lancet, 2014, 383: 1947–1948.
42. Martin RM, Vatten L, Gunnell D, *et al*. Blood pressure and risk of prostate cancer: cohort Norway (CONOR). Cancer Causes Control, 2010, 21: 463–472.
43. Yu HC, Luo YX, Peng H, *et al*. Association of perioperative blood pressure with long-term survival in rectal cancer patients. Chin J Cancer, 2016, 35: 38.
44. 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.
45. 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.

**DOI 10.1007/s10330-018-0304-4**
**Cite this article as:** Quan XY, Wang PJ, Lei L, *et al*. Analysis of clinical efficacy of P-Gemox regimen sandwich radiotherapy, P-Gemox regimen sequential radiotherapy, and radiotherapy alone treatment for extranodal natural killer/T-cell lymphoma. Oncol Transl Med, 2018, 4: 185–195.