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Optimal induction treatment regimens for extranodal NK/T-cell lymphoma: lessons learned, challenges, and proposals

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Extranodal NK/T-cell lymphoma (ENKTCL) is a highly aggressive and Epstein-Bar virus (EBV)-associated hematologic malignancy, most prevalent in the Far East and South America [1]. No standard treatment strategy has been defined. It is well recognized that combination of asparaginase-based chemotherapy (CT) and radiotherapy (RT) benefit early-stage ENKTCL. It has been validated that upfront RT can cure most stage I patients of ENKTCL without risk factors, and asparaginase (either L-asparaginase or pegaspargase) is the backbone of chemotherapy for ENKTCL. In recent years, a variety of asparaginase-based regimens have been found to be effective in early-stage ENKTCL, such as GELOX (gemcitabine, oxaliplatin, and asparaginase) [2] or EPOCHL (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and asparaginase) [3], but with different toxicities. Thus, we are wondering how much is too much for early-stage ENKTCL patients, and is intensive chemotherapy really necessary? Moreover, the international T-cell Project reported the updated survival outcomes of a large cohort of worldwide patients with ENKTCL (except Chinese) this year, and more than 60 regimens were used in this report, indicating a lack of standard treatment regimens [4]. Compared with the survival data of Chinese patients with ENKTCL, the outcomes reported by this international multi-center cohort seem unsatisfactory. Due to very small number of patients enrolled from the USA and no patients from China, it is of importance to show the data from these two large countries, which enable us to depict the real-world data of ENKTCL globally. In this multi-center retrospective study, we compared the efficacy, long-term survival outcomes, and safety profiles between GELOX and EPOCHL regimen in early-stage ENKTCL patients. Meanwhile, the survival outcomes of all-stage patients from China and SEER (Surveillance, Epidemiology, and End Results) database were compared.

A total of 494 patients of ENKTCL with all stages (Ann-Arbor stage I, $n = 224$; stage II, $n = 168$; stage III-IV, $n = 102$) from Beijing Tongren Hospital were included in this study, and all patients received asparaginase-based treatment, among whom 193 patients with stage I-II ENKTCL were treated with 4-6 cycles of GELOX (pegaspargase 2,500 IU/m^2 d1, gemcitabine 1,000 mg/m^2 d1, 8, oxaliplatin 100 mg/m^2 d1, repeated every 3 weeks) or EPOCHL (etoposide 50 mg/m^2/d, vincristine 0.5 mg/d, doxorubicin 10 mg/m^2/d were administered by continuous intravenous infusion over 96 h d1-4, prednisone 60 mg/m^2/d was administered orally on days 1-5, cyclophosphamide 750 mg/m^2 was given as an intravenous bolus on day 5, L-asparaginase 10,000 U/d was administered by intravenous infusion on days 6-10 or pegaspargase 2500 IU/m^2 d1, repeated every 3 weeks) regimen combined with radiotherapy (≥ 50Gy), either sequential or sandwich chemoradiation. Response to treatment was evaluated using MRI scan or PET-CT scan after chemotherapy and end of treatment. Progression free survival (PFS) was calculated from diagnosis of ENKTCL to disease progression, death of any reason, or last follow-up, whichever came first. Overall survival (OS) was defined from diagnosis to death of any reason, or last follow-up, whichever came first. The institutional ethics review board approved this study and all patients provided informed consent for publication of clinical data at their first visit, but all patients in this study had been de-identified. Moreover, we identified 1140 patients with ENKTCL from the SEER database (www.seer.cancer.gov) based on the ICD-O-3 code for histology (9719, ENKTCL) from 1987 to 2015, and 330 patients were excluded from our analysis due to unknown stage or missing detailed survival data.

68 patients with early stage ENKTCL received GELOX induction therapy and 125 patients were treated with EPOCHL regimen. No significant difference was found between those two groups concerning baseline character-

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istics. At the end of treatment, a complete response (CR) rate of 75% and an overall response rate (ORR) of 98.5% was achieved in the GELOX group, and the CR rate and ORR were 56% and 94.4% in the EPOCHL group, respectively. Although there was no significant difference in ORR between GELOX and EPOCHL regimen, as is shown in Figure 1, patients treated with GELOX had significantly better PFS and OS than those with EPOCHL ($P < 0.05$). Meanwhile, the safety profile of GELOX regimen was more favorable than EPOCHL, especially the hematology toxicities. As expected, patients with stage II disease had significantly inferior outcomes than those with stage I disease ($P < 0.05$). The end of treatment efficacy had a significant impact on the long-term survival outcomes, as patients with CR enjoyed more favorable PFS and OS than those without CR ($P < 0.05$). In the GELOX cohort, efficacy assessment data was available before RT consolidation. As is shown in Figure 1-H, patients without CR after induction chemotherapy had significantly inferior PFS than those with CR ($P = 0.033$), though part of those patients could be salvaged by RT consolidation and attained CR at the end of RT.

The detailed baseline characteristics of both Chinese and SEER cohorts were shown in Table 1. More patients in the SEER database were treated before 2010 when asparaginase-based therapies were not well recognized. More-

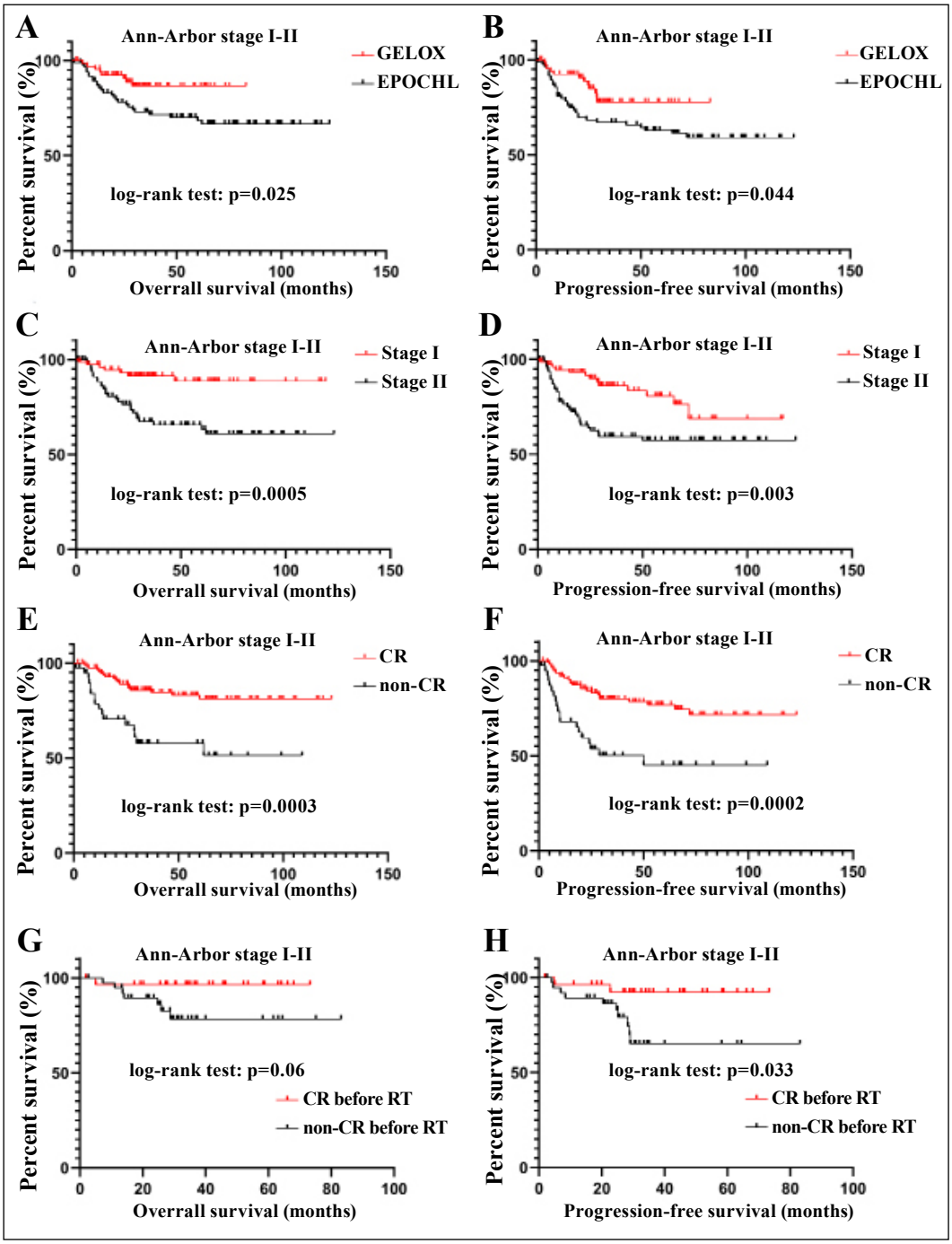

Figure 1. Survival curves for ENKTCL patients with localized disease. Patients treated with GELOX regimen had significantly better OS **(A)** and PFS **(B)** than those treated with EPOCHL. Patients with stage II disease had significantly inferior OS **(C)** and PFS **(D)** than those with stage I. The end of treatment response significantly correlated with prognosis of ENKTCL **(E, F)**. For patients treated with GELOX, CR before radiotherapy indicated significantly better PFS **(H)** and a trend for better OS **(G)**. CR means complete response, RT means radiotherapy.

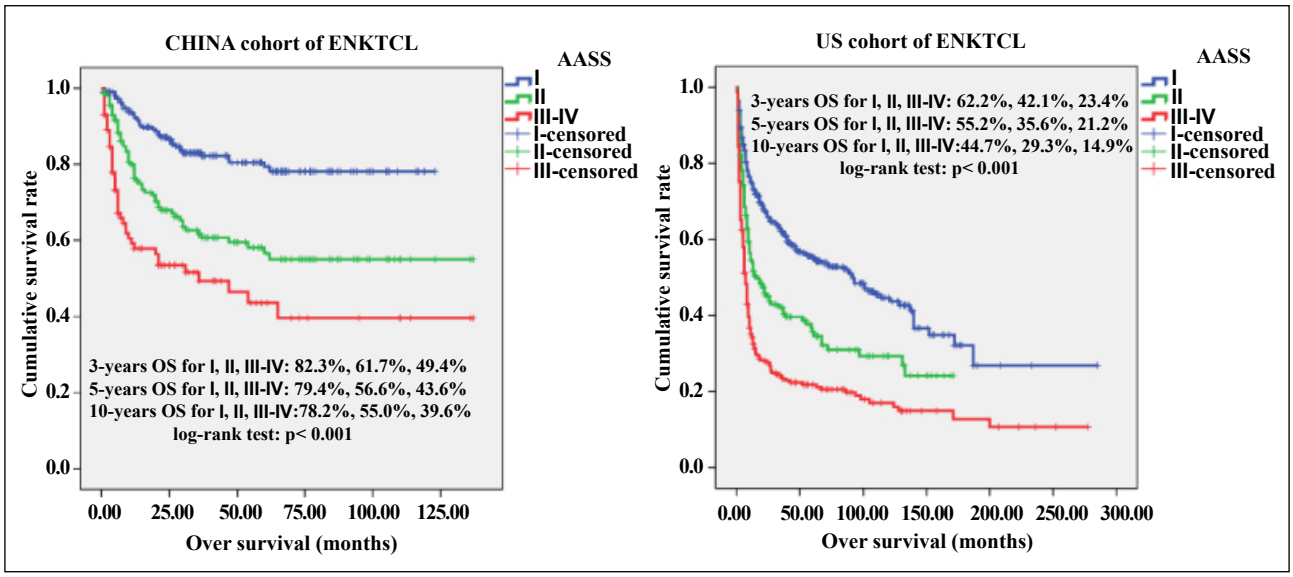

Figure 2. Survival curves for patients of ENKTCL in the Chinese **(A)** and SEER **(B)** cohorts. AASS means Ann-Arbor staging system.

Table 1. The baseline characteristics of ENKTCL patients.

	Chinese cohort (N = 494)	SEER database (N = 241)	P-value
Year of diagnosis			
1987-2009	191 (38.7%)	443 (54.7%)	$P < 0$ .001
2010-now	303 (61.3%)	367 (45.3%)	
Gender			
Male	335 (67.8%)	524 (64.7%)	$P = 0.274$
Female	159 (32.2%)	286 (35.3%)	
Age			
<60	403 (81.6%)	513 (63.3%)	$P < 0.001$
≥60	91 (18.4%)	297 (36.7%)	
Ann-Arbor stage			
I	179 (36.2%)	381 (47.0%)	
II	197 (39.9%)	179 (22.1%)	$P < 0.001$
III-IV	118 (23.9%)	250 (30.9%)	
Primary lymphoma site			
UADT	452 (91.5%)	596 (73.6%)	$P < 0.001$
Non-UADT	42 (8.5%)	214 (26.4%)	
Nasal cavity	320 (64.8%)	387 (47.8%)	$P < 0.001$
Extra-nasal sites	174 (35.2%)	423 (52.2%)	

over, significantly more patients in the SEER database had extra-nasal or non-upper aerodigestive tract (UADT) disease. The treatment strategies were unknown for the SEER database, and asparaginase-based chemotherapy with or without combined radiotherapy was administrated in the Chinese cohort. As is shown in Figure 2, the five-year OS rate was 79.4%, 56.6%, and 43.6% for patients with stage I, II, and III-IV, respectively, in the Chinese cohort, which seemed much better than that in the SEER database (55.2%, 35.6%, and 21.2%, respectively). This discrepancy may be caused by unbalanced baseline characteristics and different treatment strategies. Also, the etiology and biology of ENKTCL may differ between Asian and Western countries.

Due to the distinct geographic pattern of ENKTCL, many studies were done in Asian countries, and asparaginase-based induction therapies were well recognized, should be given in the first-line setting. Nowadays, risk-model guided therapy should be implemented in clinical practice [5]. For those localized diseases at low-risk, radiotherapy alone could achieve satisfactory results, and asparaginase-based chemotherapy should be added to radiotherapy for those with risk factors. The standard induction regimens were not defined yet, and our previous study demonstrated that pegaspargase monotherapy in combination with concurrent radiotherapy could attain 100% CR rate for early stage disease [6], which needs to be validated in phase 3 RCTs. Although the prognosis is much better for the Chinese cohort, patients with the advanced disease still fare poorly. Increasing evidence has shown the advantage of immunotherapy (PD-1/PD-L1 blockade) in relapsed/refractory ENKTCL [7], and we guess the first-line use of immunotherapy in combination with asparaginase-based chemotherapy might further improve the prognosis of patients with advanced disease [8]. Recently, a novel molecular subtyping system was defined for ENKTCL, including TSIM, MB, and HEA subtypes, with both prognostic value and treatment guidance [9]. In the future, prospective clinical trials should be conducted incorporating the new risk models and molecular subtyping system, to further implement precision medicine in ENKTCL.

Declarations

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