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Hematologic Malignancies

Pegaspargase Combined with Concurrent Radiotherapy for Early-Stage Extranodal Natural Killer/T-Cell Lymphoma, Nasal Type: A Two-Center Phase II Study

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Extranodal NK/T-cell lymphoma • Chemoradiotherapy • Pegaspargase

Abstract

Background. Concurrent chemoradiotherapy (CCRT) is expected to improve local and systemic disease control and has been established as a standard therapy for several types of solid tumors. Considering the benefits of frontline radiation and pegaspargase in localized extranodal natural killer (NK)/T-cell lymphoma, nasal type (ENKTL), we conducted a phase II study on pegaspargase-based CCRT to explore an effective treatment.

Materials and Methods. In this study, 30 patients with newly diagnosed nasal ENKTL in stages IE to IIE received CCRT (radiation 50 Gy and two cycles of pegaspargase 2,500 unit/m^2 every 3 weeks). Four courses of pegaspargase were performed after CCRT.

Results. The patients completed CCRT and four cycles of pegaspargase. The complete remission (CR) rate was 90%, with a 95% confidential interval (CI) of 73.5%–97.9% after CCRT. The CR rate was 100% (95% CI, 88.4%–100%) at the end of the treatment. The 2-year overall survival and progression-free survival rates were 90.9% (95% CI, 78.4%–100%) and 92.8% (95% CI, 83.2%–100%), respectively. The major adverse events were in grades 1–2.

Conclusion. Preliminary data indicate that pegaspargase combined with concurrent radiotherapy for newly diagnosed patients with nasal ENKTL was efficacious and well tolerated. *Registered at* www.chictr.org. *Clinical Trial Registration Number. ChiCTR-OIC-15007662*. ***The Oncologist*** 2020;25:e1725–e1731

Implications for Practice: This clinical trial, evaluating the efficacy and toxicity of concurrent chemoradiotherapy by using single-drug pegaspargase for patients with extranodal natural killer/T-cell lymphoma, nasal type (ENKTL) in stage IE to IIE, showed pegaspargase combined with concurrent radiotherapy was efficacious and well tolerated. Pegaspargase has a long half-life and is easy to administer via intramuscular injection. Consequently, pegaspargase combined with concurrent radiotherapy for patients with ENKTL can be completed in the outpatient clinic.

Background

Extranodal natural killer/T-cell lymphoma, nasal type (ENKTL) is a rare and special type of non-Hodgkin's lymphoma (NHL), mainly involving extranodal organs, especially upper respiratory and digestive tracts [1, 2]. In view of the low incidence of nasal ENKTL, an international multicenter and randomized controlled clinical study has yet to be performed to explore the best treatment for nasal ENKTL. Most reports involve retrospective analysis or prospective phase I/II clinical studies

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with a small sample size. Therefore, the best treatment for nasal ENKTL remains unclear. Radiotherapy (RT) has been widely used for early lesions, and rapid remission can be achieved [3, 4]. However, radiotherapy alone is no longer recommended for the treatment of early nasal ENKTL. Approximately one-half of patients receiving radiotherapy alone will have local recurrence, and nearly 25% of patients will have distant metastasis and recurrence [5, 6]. Concurrent chemoradiotherapy (CCRT) is expected to reduce the local and systemic recurrence rate. In a phase I/II clinical study conducted by the Japanese Clinical Oncology Group (JCOG0211), dexamethasone, etoposide, ifosfamide, and carboplatin (DeVIC) chemotherapy was selected for CCRT among patients with localized nasal ENKTL [7, 8]. However, hematological toxicity and infection were frequent, and severe radiation-induced oral mucosal inflammation was common in this study [7, 8]. Therefore, a chemotherapeutic regimen that can be concurrently performed with radiotherapy should be explored to ensure the efficacy and low toxicity of the treatment.

Asparaginase is used in several nasal ENKTL chemotherapy regimens, including gemcitabine, oxaliplatin, and L-asparaginase (GELOX) [9], glucocorticoid, methotrexate, ifosfamide, L-asparaginase, and etoposide [10] and L-asparaginase, vincristine, and prednisone [11], which produced promising results [9, 11–13]. This finding may be because asparaginase is not affected by P-glycoprotein. Evidence from previous studies showed that P-glycoprotein is highly expressed in NKTL, leading to chemotherapy resistance and reduced treatment efficiency [14, 15]. Asparaginase has a unique antitumor mechanism. NK/T lymphoma cells cannot synthesize asparagine, which is essential for growth and must rely on host supply. Asparaginase products can hydrolyze asparagine, resulting in its absence from cancer cells and inhibiting cancer growth [16]. Multiple studies have reported that the efficacy of asparaginase-based regimen is significantly better than that of nonasparaginase-based regimen in the treatment of newly diagnosed nasal ENKTL [17–19]. Hence, asparaginase may be a promising option in the treatment of nasal ENKTL. Besides, pegaspargase is a noncytotoxic drug with low blood toxicity. It usually does not aggravate radiotherapy-related oral mucositis and results in promising a outcome for NKTL [9]. Pegaspargase has a long half-life and is easy to administer via intramuscular injection [17, 20]. Therefore, the treatment could be completed in the outpatient clinic.

Therefore, to reduce the toxicity of CCRT, our group conducted a prospective phase II clinical study to evaluate the efficacy and toxicity of CCRT by using single-drug pegaspargase for patients with nasal ENKTL in stage IE to IIE.

Subjects, Materials, and Methods

Eligibility Criteria

A total of 30 patients with nasal ENKTL were enrolled in two three-A hospitals in China (Sun Yat-sen University Cancer Center, The Affiliated Hospital of Hainan Medical College) from January 2016 to August 2019. The inclusion criteria were as follows: (a) biopsy-proven and previously untreated patients with nasal ENKTL; (b) Ann Arbor stage IE or IIE [21, 22]; (c) over 18 years old; (d) estimated survival time over 3 months; (e) Eastern Cooperative Oncology Group performance score 0–2; and (f) adequate hematological function (e.g., absolute neutrophil count >1.5 × 10^9 per L and platelet count >80 × 10^9 per L), renal function (e.g., serum creatinine ≤1.5 mg/dL and creatinine clearance ≥50 mL per minute), and hepatic function (e.g., AST ≤2.5 × the upper limit of normal [ULN] and total bilirubin ≤1.5 × ULN). The diagnosis was based on the World Health Organization classification of tumors of hematopoietic and lymphoid tissues. The diagnosis was determined on the basis of the histological characteristics and immunophenotypes in accordance with nasal ENKTL [23]. The exclusion criteria included prior or coexisting malignant tumors and any medical problems that might result in poor compliance with the study protocol. ENKTL in the absence of nasal disease with the primary tumor at other sites, such as gastrointestinal tract or skin, was excluded.

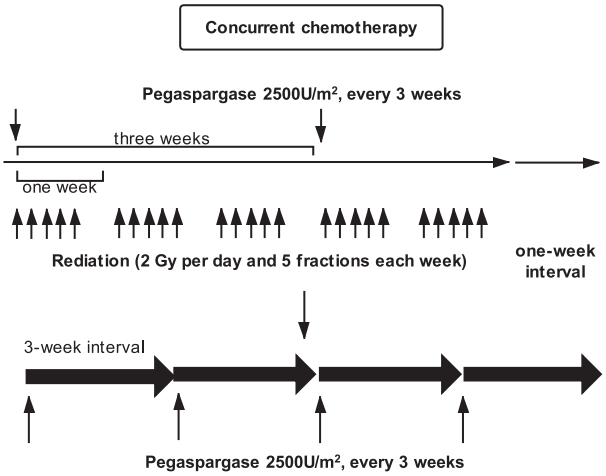

Figure 1. Concurrent chemoradiotherapy.

Treatment and Dose Modifications

The treatment scheme (Fig. 1) consisted of CCRT followed by four cycles of pegaspargase. The treatment was administered in the outpatient clinic. Chemotherapy and RT were performed simultaneously within one week after enrollment. The drug administration schedule was as follows: day 1, deep intramuscular injection of 2,500 unit/m^2 pegaspargase at three different sites. Chemotherapy was repeated every 3 weeks. Pegaspargase was administered when the plasma fibrinogen level was >0.75g/L. Otherwise, treatment was delayed and human fibrinogen or cryoprecipitate was supplemented. Granulocyte colony-stimulating factor was administered when grades 3–4 neutropenia occurred. If drug-related acute pancreatitis developed, chemotherapy was terminated. The acute pancreatitis was defined as (a) symptoms of acute pancreatitis, (b) blood amylase/lipase >3 × ULN, (c) results of imaging examination suggest acute pancreatitis. Six courses of chemotherapy were performed.

All the patients received three-dimensional conformal radiation therapy by using 4 or 6 MV photons generated from a linear accelerator. The involved-field radiation therapy dose was 50 Gy and administered as 2.0 Gy per daily fraction within 5 weeks. The clinical target volume (CTV) for the limited-stage IE disease was defined as the bilateral

nasal cavity, bilateral ethmoid sinuses, and ipsilateral maxillary sinus and extended to the involved tissues for patients with extensive stage IE disease [24]. The CTV of stage IIE disease also included the involved cervical lymph node area. In the course of radiotherapy, radiotherapy should be postponed until the toxicity was reduced to grade 2 or lower if the following adverse events (AEs) occurred: grade 4 leukopenia or neutropenia, platelet count below 25,000/μL, and any grade 3 or higher nonhematological toxicity except radiotherapy-related oral mucositis or dysphagia. If the toxicity did not return to grade 2 after 2 weeks, radiotherapy was terminated.

Evaluation

Baseline evaluation was completed within 1 week before enrollment, and this procedure included medical history, physical examination, blood routine and biochemical routine with lactate dehydrogenase (LDH), bone marrow aspiration smear and biopsy, nasopharyngeal and neck magnetic resonance imaging (MRI), and whole-body positron emission tomography-computed tomography (PET/CT) scan. The detection of Epstein-Barr virus (EBV) DNA copies in the plasma was completed via quantitative polymerase chain reaction. All patients were staged on the basis of the Ann Arbor staging system. Nasopharyngeal and neck MRI, whole-body PET/CT, and detection of EBV-DNA copies were performed in the evaluations after treatment and the follow-up for all patients. The first evaluation after treatment was performed 1 week after RT, before the third administration of pegaspargase. During the follow-up, assessments including nasopharyngeal and neck MRI, whole-body PET/CT, and detection of EBV-DNA copies were repeated every 3 months for the first 2 years. After 2 years, the evaluations were repeated every 6 months to monitor disease progression.

Response and Toxicity Criteria

Treatment response was assessed in accordance with the standard response criteria for NHL after CCRT [25], four and six cycles of pegaspargase. Lugano criteria [22] was used to re-evaluate all the patients, and the results of treatment response were consistent. After four cycles of pegaspargase, patients who did not obtain complete response (CR) could withdraw from the study and receive salvage chemotherapy. The primary endpoint was the CR rate and toxicity. All the adverse effects after CCRT and chemotherapy were graded in accordance with the National Cancer Institute Common Terminology Criteria Adverse Events version 3.0 [26]. The secondary end points were 2-year progression-free survival (PFS) and 2-year overall survival (OS). PFS was defined as the time from diagnosis to disease progression. OS was calculated from the date of diagnosis to the date of death for any reason. PFS and OS were censored at the time of the last follow-up visit.

Statistical Analysis

The CR rate of radiotherapy alone ranged from 60% to 80% for stages IE to IIE nasal ENKTL [4, 6, 27, 28]. Therefore, sample size was calculated to be adequate to reject a 70% CR rate in support of a target CR rate of 90% on the basis of Simon's optimal two-stage design. At the first stage, six patients should be accrued. If the number of patients with CR amongst these patients was four or more, the study would continue to enroll patients. Afterward, 21 patients

Table 1. Patient demographic and clinical characteristics

Characteristic	Patients, *n* (%)
Age, yr	
≤60	27 (90.0)
>60	3 (10.0)
Sex	
Male	19 (63.3)
Female	11 (36.7)
ECOG performance status	
0–1	27 (90.0)
2	3 (10.0)
Ann Arbor stage	
I	18 (60.0)
II	12[a] (40.0)
Serum LDH	
Normal	22 (73.3)
Increased	8 (26.7)
"B" symptoms[b]	
Absent	19 (63.3)
Present	11 (36.7)
EBV-DNA, median (range), copies/mL	222.50 (0–3.42 × 10^5)
<1,000	18 (60.0)
≥1,000	12 (40.0)
LN involvement	
Absent	22 (73.3)
Present	8[a] (26.7)
Absolute lymphocyte count	
≥1,000/mm^3	23 (76.7)
<1,000/mm^3	7 (23.3)
Hemoglobin level	
≥120g/L	20 (66.6)
<120g/L	10 (33.3)
IPI score	
0-1	23 (76.6)
2–5	7 (23.4)
PINK score	
Low risk	27 (90.0)
Intermediate risk	3 (10.0)
High risk	0 (0)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; IPI, International Prognostic Index; LDH, lactate dehydrogenase; LN, lymph node; PINK, prognostic index for natural killer lymphoma.

[a]4 patients had lesions in the orbit (*n* = 1), oropharynx (*n* = 2), and lower lip (*n* = 1) besides lesions in the nasal cavity. Although no lymph node invasion was found, discontinuous violations are also recognized as stage II, according to the Ann Arbor system. Therefore, although 8 patients had nodal involvement, 12 patients had Ann Arbor stage II.

[b]B symptoms include unexplained fever with temperature above 38°C, night sweating or weight loss more than 10% within 6 months.

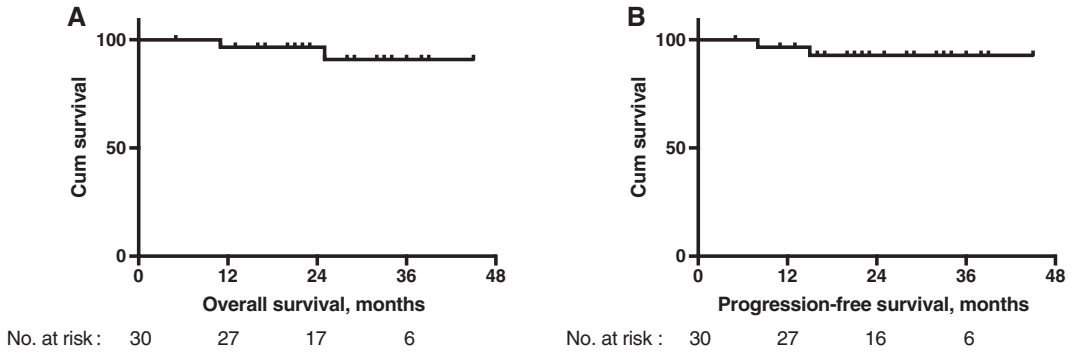

Figure 2. Survival curves. **(A):** Two-year OS rate was 90.9%. **(B):** Two-year PFS rate was 92.8%.

were scheduled to be enrolled. Finally, if CR was observed in 22 or more patients, the treatment would continue into the phase III trial. In consideration of the 10% dropout rate, the total sample size of 30 patients was required. PFS and OS were calculated using the Kaplan-Meier method and compared using the log-rank test. If a two-sided *p* value was <.05, differences were considered significant.

Results

Patient Characteristics

Baseline patient characteristics are summarized in Table 1. The immunohistochemical analysis of tumor tissues showed that 30 patients expressed cytoplasmic CD3, and 28 patients (93.3%) expressed CD56. T-cell intracellular antigen was positive in all the 30 cases (100%). EBV RNA was subjected to in situ hybridization, and all of the 30 patients expressed EBV-encoded small RNA. In this prospective cohort, the mean age was 46 years (range, 26–75), and three patients (10.0%) were over 60 years. Of the 30 patients, 63.3% were male. B symptoms were observed in 11 patients (36.7%), and increased LDH levels were found in 8 patients (26.7%). Twelve patients had an increased EBV viral load at baseline (40%). Local regional lymph nodes were present in eight patients (26.7%). According to international prognostic index (IPI), most of the patients (23 cases, 76.6%) were categorized as low risk (IPI = 0–1). Three patients (10.0%) belonged to an intermediate-risk group, and none belonged to the high-risk group according to the PINK score, which included age over 60 years, stage III or IV disease, distant lymph node involvement, and non-nasal type disease [29].

Response to Treatment and Survival

All the patients completed two cycles of pegaspargase with CCRT followed by four cycles of pegaspargase. No radiotherapy or chemotherapy was delayed because of toxicity. Consequently, compliance with the planned treatment regimen was 100%. Of the 30 patients evaluable for response, 27 patients with CR (90.0%; 95% confidence interval [CI], 73.5%–97.9%) and 3 patients with PR were recorded after CCRT. CR was achieved in all the patients at the end of treatment (100%; 95% CI, 88.4%–100%), and all of them were included in the survival analysis. The median follow-up time for the 30 patients evaluated in this cohort was 26.5 months, with a range of 5–45 months. In these patients, the 2-year OS and PFS rates were 90.9% (95% CI, 78.4 %–100%; Fig. 2A) and 92.8% (95% CI, 83.2%–100%; Fig. 2B), respectively. During the follow-up period, 2 of the 30 patients experienced disease recurrence. After 4 months of treatment, one patient (a 55-year-old man) experienced a systemic relapse with several skin lesions on the right arm and the thigh. He refused salvage therapy and died 3 months later. Local disease relapse was observed in one patient (a 43-year-old woman), who experienced a relapse in the left maxillary sinus within the previous field of radiotherapy. Although the patient was treated by a variety of salvage chemotherapy regimens, including gemcitabine, oxaliplatin, and pegaspargase and etoposide, vincristine, doxorubicin, cyclophosphamide, and prednisone [17, 30], she died 10 months after relapse.

Table 2. Adverse events observed from treatment and event grade

	No. of events by grade			
Adverse event	**1**	**2**	**3**	**4**
Hematologic				
Leukopenia	9	7	4	0
Anemia	13	9	1	0
Thrombocytopenia	2	0	0	0
Nonhematologic				
Mucositis related to radiation	13	8	0	0
Nausea	4	2	0	0
Vomiting	1	0	0	0
Anorexia	9	3	0	0
Hyperbilirubinaemia	8	3	0	0
Increased transaminases	15	3	0	0
Hypoalbuminemia	12	11	2	0
Decreased fibrinogen	3	7	7	0
Hyperglycemia	0	0	0	0
Thrombosis	0	0	0	0

Toxicity

Table 2 summarizes grade 1–4 toxicities for the 30 patients enrolled in the phase II study. The major AEs were leukopenia, anemia and mucositis related to radiation, hepatic dysfunction, decreased fibrinogen, and hypoalbuminemia in grade

1–2. Grade 4 toxicity was not recorded during treatment. Thrombocytopenia occurred only in two patients and was in grade 1. A total of seven (n = 7) patients were confirmed to have decreased fibrinogen in grade 3 and treated with freshly frozen plasma and human fibrinogen. No thrombotic adverse events, bleeding, or other AEs were observed. No treatment was interrupted for severe AEs, and no treatment-related deaths occurred. Thus, the treatment regimen had a relatively low toxicity, and patients had good tolerance for this treatment.

Discussion

To our knowledge, our study is one of the few prospective studies of CCRT for newly diagnosed nasal ENKTL in stages IE to IIE. This study explored the frontline treatment with CCRT followed by pegaspargase for nasal ENKTL in stages IE to IIE. Pegaspargase was administered once every 3 weeks as a radiosensitizer to improve the effects of radiotherapy on CCRT. The CR rate after CCRT was 90.0%, and the CR rate at the end of treatment was 100%. With a median follow-up of 26.5 months, the 2-year OS and PFS rates were 90.9% and 92.8%, respectively. The toxicities were mild, and no treatment-related deaths occurred. Thus, pegaspargase combined with CCRT was effective with low toxicity amongst patients with newly diagnosed nasal ENKTL in stage IE/IIE.

Another prospective study of early-stage ENKTL was carried out in our center with GELOX chemotherapy followed by radiotherapy [9]. The baseline characteristics of the patients were roughly the same compared with our study. In both studies, most patients were under 60 years and male. Nearly one-third of all patients had B symptoms. A total of 11.1%–26.7% of patients had increased LDH levels. Most patients were low risk in both studies [9]. In the GELOX study, the CR rate was 74.1%, and the 2-year overall and progression-free survival rates were both 86% at a median follow-up of 27.37 months [9]. In our study, the CR rate was 100%, and the 2-year OS and PFS rates were 90.9% and 92.8%. Besides, the CR rate after CCRT was 90.0% in our study, which is considerably higher than the rates reported in previous studies on CCRT, radiotherapy alone, and chemotherapy followed by radiotherapy [7, 11, 12, 27, 28, 31, 32]. Therefore, we considered our therapeutic regimen to be highly effective for the treatment of localized nasal ENKTL.

Radiotherapy remains the cornerstone of ENKTL treatment. The synchronized use of some systemic therapies based on radiotherapy enhanced radiosensitization and cleared the minimal disease outside the field of radiotherapy to reduce local recurrence and distant recurrence. Platinum-based drugs can sensitize radiotherapy, which has been reported in solid tumors [33–35]. Prior to this finding, two studies have used concurrent platinum monotherapy or platinum-containing chemotherapy with radiotherapy followed by chemotherapy for early nasal ENKTL. In the study of DeVIC combined with concurrent radiotherapy, 30% of the patients developed third-degree radiation-related mucositis, and more than 90% developed third or fourth-degree granulocytopenia [7, 8]. In the study of concurrent radiation and weekly cisplatin followed by etoposide, ifosfamide, cisplatin, and dexamethasone (VIPD) chemotherapy, although only one patient experienced grade 3 toxicity during CCRT (nausea), 41.4% of the patients experienced grade 4 hematological toxicity [31]. The common disadvantage of these two CCRT schemes is that the toxicity of treatment is high and that patients are not easily tolerated. In fact, in multiple studies on CCRT with nonanthracycline chemotherapy for newly diagnosed localized ENKTL, 15%–83% of the patients experienced grade 4 leukopenia [36]. We attempted to use the GELOX regimen for treating early nasal ENKTL with CCRT. However, the study was terminated because of the treatment's high toxicity, especially in the oral mucosa. In our study, the major AEs were in grades 1–2, and no grade 4 toxicities were recorded during treatment. A relatively high incidence of grade 3 adverse reactions involved a decrease in fibrinogen, but no bleeding or other discomfort was recorded after the corresponding supplementation. The results suggested that pegaspargase combined with CCRT had low toxicity among patients with nasal ENKTL compared with other CCRT regimens.

Radiotherapy is an essential part of the frontline treatments for NKTL. The optimal dose of radiotherapy has not yet been determined, especially in CCRT regimens. The dosage in CCRT regimens ranges between 36 and 56 Gy. The CCRT regimens with a median radiotherapy dosage of 40 Gy reached a CR rate of 80%–87% [31, 37, 38]. Meanwhile, the CCRT regimens with a median dosage of 50 Gy reached a CR rate of 63%–77% [7, 8, 39]. It appears that a higher dose of radiotherapy may not contribute more to a good outcome. In our study, the radiotherapy dose was 50 Gy, with a CR rate of 90% after CCRT. Future studies may explore the efficiency and safety of CCRT regimens containing a lower dose of radiotherapy.

Four courses of pegaspargase were added to the regimen to prevent systemic relapse and for consolidation. Three patients achieved PR and experienced conversion to CR after pegaspargase chemotherapy, resulting in a 100.0% CR rate. Furthermore, only two patients experienced relapse during follow-up: one was local and one was systemic recurrence. Patients with systemic recurrence were characterized by a high Ki67 index and lactate dehydrogenase, suggesting that some high-risk patients might need multidrug combination chemotherapy. Still, the local and systemic relapse rates were both only 3.3%. A previous prospective study on 30 patients treated with concurrent radiation and weekly cisplatin followed by VIPD (nonasparaginase-based) chemotherapy reported a high systemic relapse rate (10%) [31]. Another prospective trial of CCRT shows a distant disease recurrence rate of 33% (9 of 27) [7, 8]. We speculated that the low systemic recurrence rates in our study were associated with high complete remission rates after CCRT. This finding may be a consequence of the synergistic effect of pegaspargase and radiotherapy. Pegaspargase chemotherapy as an adjuvant to CCRT may help prevent relapse and deepen the response achieved by CCRT.

Previous researchers showed that post-treatment and pretreatment EBV-DNA level is predictive of treatment response and outcome for NKTL [40–42]. In our study, 12 patients had increased EBV-DNA copies at baseline. Eleven of the 12 patients reduced to a normal EBV viral load after treatment. One patient's EBV-DNA copies remained above 1,000 after treatment, and this patient experienced systemic recurrence within

6 months. Of 11 patients reducing to a normal EBV load, only one patient relapsed after one year. The cases were too few to perform statistical analysis. However, to a certain level, it revealed that EBV-DNA copies are predictive of patients' recurrence. The conclusion was consistent with previous researches [40–42].

There were some limitations in our study. The sample size was small, and the follow-up time was short. Therefore, a phase III clinical trial is not yet planned. Despite the limited sample size and follow-up period, enthusiastic results were obtained.

Conclusion

The results of this phase II study indicate that pegaspargase combined with CCRT is an effective and safe treatment for patients with newly diagnosed nasal ENKTL with stage IE to IIE. Further investigation on large prospective trials should be conducted to confirm our findings.

Acknowledgments

We thank the patients and their families and all the investigators, including the physicians, nurses, and laboratory technicians in this study.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the ethics committee and the institutional review board of Sun Yat-Sen University Cancer Center and The Affiliated Hospital of Hainan Medical College with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

This article contains no individual person's data in any form.

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Disclosures

The authors indicated no financial relationships.

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