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ORIGINAL ARTICLE

Efficacy of different regimens in nasal NK/T-cell lymphoma and analysis of serum inflammation and prognosis of patients

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Summary

Purpose: *To explore the efficacy of different regimens in nasal natural killer (NK)/T-cell lymphoma (NNKTL) and their effects on the serum inflammation and prognosis of patients.*

Methods: *146 NNKTL patients admitted to and treated in the Oncology Department of our hospital from January 2010 to December 2014 were randomly enrolled and divided into chemotherapy group (group A) and concurrent chemoradiotherapy group (group B). The expression levels of interleukin-2 (IL-2) and tumor necrosis factor-alpha (TNF-a) before and after treatment were detected, the short-term efficacy was followed up and analyzed, and the correlation between the two was statistically analyzed.*

Results: *In group A and group B, the total short-term effective rate was 71.87% and 84.97%, the 5-year overall survival (OS) rate was 39.9% and 66.2%, and the progression-free survival (PFS) rate was 18.1% and 46.9%, respectively. Treatment regimens, clinical stage, the presence of B symptoms and lactate dehydrogenase (LDH) level were independent factors related to prognosis, and the remission rate after the first-course chemotherapy was an independent factor unrelated to prognosis. After treatment, there was no significant difference in the IL-2 level between the two groups of patients before and after treatment. The expression level of TNF-a after treatment was reduced compared with that before treatment, and the reduction was more obvious in group B.*

Conclusions: *The short-term efficacy of concurrent chemoradiotherapy favors NNKTL, and the therapy can reduce the expression level of TNF-a.*

Key words: *nasal NK/T-cell lymphoma, efficacy, IL-2, TNF-a*

Introduction

Nasal type extranodal NT/T-cell lymphoma (ENKTL), namely NNKTL, is a relatively rare lymphoma with high malignancy [1]. NNKTL derives from the nasal cavity and frequently occurs in the nasal septum and lower nasal cavity. With the progression of disease, patients have nasal space-occupying lesions, which extensively involve adjacent soft tissues, ulcers and bone destruction [2]. NNKTL affects the skin, gastrointestinal tracts and reproductive organs with various manifestations [3].

At present, ENKTL patients are mainly treated by chemotherapy, radiotherapy or blood stem cell transplantation. Radiotherapy produces relatively good efficacy in the early stage but poor efficacy in advanced stages. NNKTL has unique epidemiological, etiological, histological and clinical characteristics. It is common in East Asia but rare in the United States and Europe [4]. Phenotypic and genotypic studies have revealed that lymphoma originates from NK cells or γδT cells that express CD56 [5]. In 1990, researchers reported the existence of Epstein-Barr virus (EBV)-deoxyribonucleic acid (DNA) and EBV-oncoprotein for the first time. Currently, EBV has been confirmed to play a pathogenic role in NNKTL [6]. It has been manifested in *in*

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vitro studies that diversified cytokines, chemokines and micro ribonucleic acid (miRNAs) may be produced by EBV-oncoproteins in lymphoma cells, and the EBV-oncoproteins play a vital role in the progression of NNKTL tumors and can be used as therapeutic targets. Besides, it has also been discovered that the interaction between NNKTL cells and immune cells, such as monocytes and macrophages, facilitates the progression of lymphoma [7]. It is of great significance to detect EBV-DNA and EBV-miRNA in serum for the diagnosis, clinical process monitoring and prognosis prediction. The prognosis of NNKTL patients in the early stage treated with new chemoradiotherapy developed with radiotherapy, such as DeVIC scheme for local radiotherapy and MPVIC-P scheme for intra-arterial perfusion with radiotherapy, is significantly improved, but the prognosis of those in advanced stages remains poor [8, 9].

The treatment of NNKTL is a major problem in the management of ENKTL, but no consensus has been reached on the treatment of local NNKTL. At present, recommended treatment methods are mainly based on the results of phase II studies and retrospective analyses, and there is no standard treatment on the basis of randomized controlled trials. In this paper, the treatment regimens for 146 NNKTL patients were retrospectively compared and analyzed, and the efficacy and prognosis of these regimens were analyzed, so as to provide certain guidance for NNKTL treatment.

Table 1. General data of patients

Item	*n (%)*
Gender	
Male	70 (47)
Female	76 (53)
Age (years)	
8-40	96 (73)
41-80	50 (27)
B symptoms	
Yes	97 (73.4)
No	49 (26.6)
IPI score	
0-1	29 (20)
2	65 (44.7)
3	33 (23.3)
4	19 (12)
Lactate dehydrogenase (LDH)	
Normal	89 (71.2)
Increase	57 (28.8)

Methods

Clinical data

A total of 146 NNKTL patients hospitalized in our hospital from January 2010 to December 2014 were collected. They were diagnosed according to the clinical diagnosis and staging criteria for NNKTL.

This study was approved by the Ethics Review Committee of our hospital, and all patients involved in the study signed written informed consent. The general data of the patients are shown in Table 1.

Treatment regimens

The patients were divided into chemotherapy group (group A) and concurrent chemoradiotherapy group (group B) according to the treatment regimen. There were no statistically significant differences in gender, age and other basic data between the two groups of patients ($p>0.05$). Patients receiving chemotherapy only underwent CHOP chemotherapy or DVLP chemotherapy mainly with L-asparaginase. In CHOP regimen group, cyclophosphamide, epirubicin hydrochloride, vincristine and prednisone were used, while in DVLP regimen group, vincristine, prednisone, daunorubicin and L-asparaginase were utilized, with 21 days taken as a course of treatment. Patients in group A received 6 courses of treatment, while those in group B began to receive local radiotherapy after 2 courses of chemotherapy, and then continued to receive another 4 courses of chemotherapy. In radiotherapy, a linear accelerator (6 eMV) was applied, with the radiation dose of ≥50 Gy for radiotherapy alone, and median radiation dose of 45-50 Gy for chemoradiotherapy. Conventional segmentation was implemented at 2 Gy/day for 5 times/week. The stages of patients in each group are shown in Table 2.

Index detection

Before and after treatment, 5 mL of peripheral venous blood was collected and centrifuged at the radius of 15 cm and 3000 r/min for 10 min, and serum was sepa-

Table 2. Basic data of patients in different groups

Group	*Gender (Male/Female)*	*Median age*	*Stage*				*LDH (>300 U/L)*	*B symptoms*
			I	*II*	*III*	*IV*		
Group A	39/31	46	16	24	18	12	48	31
Group B	36/40	47	20	26	18	12	61	47

rated. Samples were stored at -20°C for detection according to the instructions of a Hitachi 7600 automatic biochemical analyzer. Then interleukin-2 (IL-2) and tumor necrosis factor-alpha (TNF-α) in the samples were tested using kits in strict accordance with the instructions.

Evaluation criteria

Imaging methods to evaluate the efficacy of all patients included CT or PET-CT, which was usually combined with color Doppler ultrasound and MRI when necessary. According to WHO evaluation criteria, the clinical efficacy was evaluated as complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). The objective response rate (ORR) was calculated according to the percentage of CR+PR cases among all patients. The disease control rate (DCR) was calculated by the percentage of CR+PR+SD cases among all patients. According to WHO standards for acute and subacute toxic reactions of anticancer drugs, the severity of chemotherapy-induced toxicity is classified as class I-IV. The progression-free survival (PFS) and overall survival (OS) were used to evaluate the long-term clinical efficacy. PFS is defined as the time interval from the day of chemotherapy to the day of disease progression or death. OS refers to the time interval from the day of chemotherapy to that of death or final follow-up.

Statistics

The experimental results were analyzed by SPSS 17.0 (SPSS Inc., Chicago, IL, USA). Measurement data were assessed via the t-test. The data in the same group were compared by the paired sample t-test, while those between two groups were compared using the independent sample t-test. Survival curves were plotted according to Kaplan-Meier method and log-rank test was utilized to compare survival differences between two groups. P<0.05 suggested that the difference was statistically significant.

Results

Remission rate of different treatment regimens

The short-term efficacy of patients in the two groups was analyzed, and it was found that the total short-term effective rate in group A and group B was 71.87% and 84.97%, respectively (p<0.05) (Table 3).

Survival analysis of different treatment regimens

The median survival time of the whole group was 14.1 months as of the end date of follow-up. Of the 146 patients, 87 survived and 61 died, among which 51 died of tumor progression or recurrence of NNKTL, and 10 died of cardiovascular and cerebrovascular accidents or other diseases such as respiratory tract infection. In group A and B, the 5-year OS rate was 39.9% and 66.2%, and PFS rate

Table 3. Comparison of the efficacy between the two groups of patients

Group	*n*	*CR* *n (%)*	*PR* *n (%)*	*SD* *n (%)*	*PD* *n (%)*	*Total effective rate* *n (%)*
Group A	70	24 (36.20)	18 (23.77)	8 (10.90)	20 (29.13)	27 (71.87)
Group B	76	25 (32.90)	30 (37.81)	10 (14.26)	11 (15.03)	16 (84.97)
t						0.1342
p						0.025

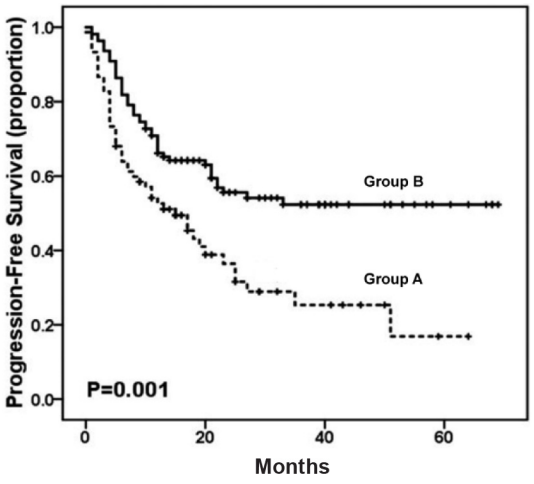

Figure 1. Comparison of PFS between the two groups of patients.

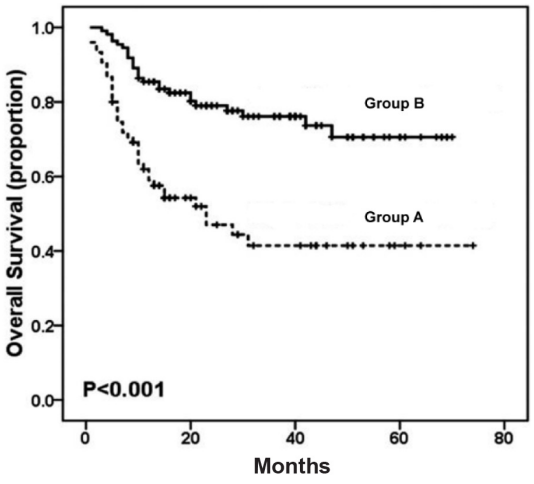

Figure 2. Comparison of OS between the two groups of patients.

was 18.1% and 46.9%, respectively. The survival analysis of the two groups of patients revealed that the 5-year OS rate in group B was higher than that in group A (p<0.05) (Figure 1,2).

Cox multivariate analysis of NNKTL

Cox proportional-hazards model was employed for multivariate analysis. The enrolled patients were divided into groups according to LDH value, Ann Arbor clinical stage, the presence of B symptoms, treatment method and whether CR was achieved after chemotherapy. The results demonstrated that treatment regimen, clinical stage, the presence of B symptoms and LDH level were independent factors associated with prognosis (p<0.05), while the remission rate after the first chemotherapy was an independent factor unrelated to prognosis (p<0.05) (Table 4).

Changes in the inflammatory factors in patients before and after treatment

The levels of inflammatory factors, IL-2 and TNF-α, in the two groups of patients before and after treatment were detected. It was found that there was no significant difference in the expression level of IL-2 between the two groups of patients before and after the treatment (p>0.05), but the expression level of TNF-α after treatment was reduced compared with that before treatment, and this reduction was more obvious in group B (p<0.05) (Figure 3).

Discussion

Currently, the pathogenesis and molecular biology of NNKTL have been gradually uncovered. Some of these findings are considered as direct evidence for the establishment of currently promising NNKTL therapy [10]. Although prospective clinical tests are required, new chemotherapy methods such as MPVIC-P and SMILE have shown good clinical efficacy [11]. Despite these achievements, the prognosis of NNKTL patients still needs to be improved by further basic research and transformation research. Cytokines or chemokines (e.g. IL-2 and TNF-α) inhibit the proliferation of NNKTL, which is an attractive method to treat NNKTL. In recent years, diverse anti-cytokine antibodies have been clinically confirmed. As revealed by Kumai et al [12], the clinical anti-CCR4 antibody Mogamulizumab is an ideal candidate drug for the treatment of NNKTL. However, the safety of these new preparations must be tested in *in vivo* models.

Zhang et al [13] searched 79 patients with early ENKTL and found that for patients with lesions in

Table 4. Cox multivariate analysis

Variables	*Regression coefficient*	*Relative risk*	*95%CI*	*p*
LDH	0.142	1.234	0.763-1.322	0.061
Clinical stage	0.481	0.781	0.653-1.011	0.411
B symptoms	1.034	2.134	1.881-2.121	0.829
Treatment regimen	1.032	2.989	2.322-3.021	0.212
CR after chemotherapy	0.263	1.437	1.221-1.612	0.011

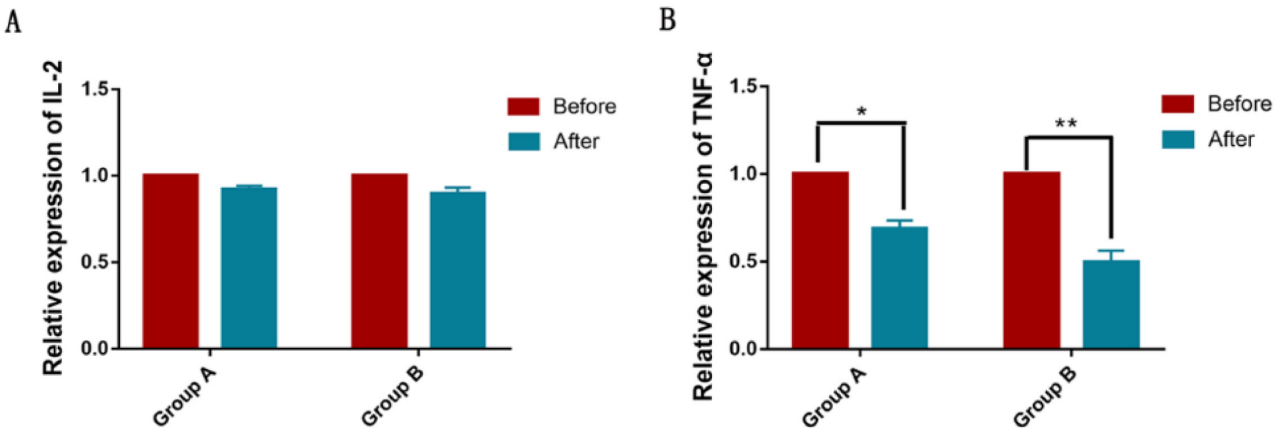

Figure 3. Changes in inflammatory factors in the two groups of patients before and after treatment: **A:** There is no significant difference in IL-2 in the two groups of patients before and after treatment (p>0.05). **B:** TNF-α in the two groups of patients after treatment is decreased compared with that before treatment (*p<0.05, **p<0.01).

the nasal cavity only, the 5-year PFS was 44.5% and 5-year OS was 46.6%. For patients with paranasal lesions, the 5-year PFS was 53.5% (p=0.734) and 5-year OS was 56.0% (p=0.613). Besides, there was no statistically significant difference in the prolonged survival time. A study of Wu et al [14] manifested that PTI (based on MRI scan) remarkably influenced the 5-year OS of 105 patients with early ENKTL (p=0.012). In their research, PTI is defined as a primary disease extending to adjacent structures or organs (e.g., the primary tumor in nasal cavity extends to the sinus and/or the nasopharynx, or involves multiple adjacent primary sites, such as the nasopharynx and oropharynx), irrespective of its stage or primary site. However, they did not find a relationship between bone or skin invasion with a significant decrease in the 5-year OS rate (p=0.087). Yan et al [15] established NNKTL TNM staging system, which can well predict the survival rate. In 271 patients, the 5-year OS of stage I, stage II, stage III and stage IV NNKTL patients was 92%, 64%, 23% and 0%, respectively. They held that their TNM staging system is very effective in the stratification of tumor burden and survival risk, and can improve the treatment decision of NNKTL patients, which is consistent with the results of the present study.

Due to the high recurrence rate after radiotherapy alone, chemoradiotherapy becomes the main treatment regimen of NNKTL. The results of this study also demonstrated that the efficacy of concurrent chemoradiotherapy was better than that of chemotherapy alone, but the 5-year survival rate was about 50% even in the early clinical stage [16-18]. To improve the efficacy, a phase I/II clinical trial (JCOG0211) including three courses of dexamethasone, etoposide, ifosfamide and carboplatin was conducted in Japan, and local NNKTL was treated by local radiotherapy (50 Gy), achieving good efficacy [19].

Bone marrow transplantation is another treatment method for NNKTL. Despite this expectation, the results of autologous or allogeneic bone marrow transplantation remain controversial [20-22]. Due to the elevation of soluble IL-2 receptor in local NNKTL pretreatment, it is necessary to improve the treatment method, so it is imperative to develop a new NNKTL treatment method.

In recent years, Takahara et al [23] developed a new arterial infusion chemotherapy from superficial temporal artery based on radiotherapy. Arterial infusion regimens include methotrexate, pepromycin, etoposide, ifosfamide, carboplatin, prednisolone (MPVIC-P), and are not affected by multidrug resistance gene 1 (except etoposide) and DeVIC regimens. Chemotherapy and concurrent radiotherapy (above 54 Gy) have 3 cycles each. The common side effects are mucositis (83%) and myelosuppression (33%), and they are controllable. Therefore, MPVIC-P regimen (intra-arterial perfusion combined with radiotherapy) is an effective method for the treatment of early NNKTL and has strong adaptive toxicity.

Conclusions

To sum up, the results of this study provide certain guidance and bases for the controversy over the treatment regimen of NNKTL in recent years, and lay a foundation for establishing the best treatment method for NNKTL patients. It is believed that further research will make NNKTL a curable disease.

Conflict of interests

The authors declare no conflict of interests.

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