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Original Article

A prospective study of chemoradiotherapy for early stage extranodal natural killer (NK)/T-cell lymphoma

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Abstract: Extranodal nasal type natural killer (NK)/T-cell lymphoma is a highly aggressive disease with poor outcome. Most data concerning nasal type NK/T-cell lymphoma was derived from small case series or retrospective analyses. This study was to investigate the efficacy of a single standard treatment method to treat extranodal NK/T-cell lymphoma, nasal type. 64 patients with early stage nasal type NK/T-cell lymphoma were randomly divided into two groups. Patients in group A (n = 30) received four cycles of cyclophosphamide, adriamycin, oncovin, prednisone (CHOP) followed by involved field radiation therapy (IF RT). Patients in group B (n = 34) received four cycles of gemcitabine, dexamethasone, L-asparaginase (GDL) followed by IF RT. Before IF RT the response rates were 50% and 88.2% for group A and B respectively (P = 0.001). And after IF RT the response rates were 93.3% and 100% respectively (P = 0.216). After median follow up of 29.5 (range 11-48) months, the median PFS was and median OS was 37.523 months versus 40.702 months, 37.255 months versus 40.558 months respectively for group A and B (log-rank test, P = 0.401 for PFS, P = 0.402 for OS), and the estimated three years progression free survival (PFS) rate was 51% versus 64% and overall survival (OS) rate was 53% versus 66%. Therefore, though different chemotherapy combined with radiotherapy cannot improve the survival of patients with early stage extranodal NK/T-cell lymphoma, the response rate of GDL chemotherapy regimen was found to be much higher than CHOP.

Keywords: Natural killer (NK)/T-cell lymphoma, cyclophosphamide, adriamycin, oncovin, prednisone (CHOP), gemcitabine, dexamethasone, L-asparaginase (GDL), involved field radiation therapy (IF RT)

Introduction

Extranodal natural killer (NK)/T-cell lymphoma, nasal type is an uncommon type of non-Hodgkin's lymphoma with relatively low incidence. The disease is much more common in Asian and Latin American countries than in Western countries, and it is universally associated with epstein-barr virus (EBV) infection [1-3]. It is an aggressive entity of non-Hodgkin lymphoma with distinctive clinicopathologic features that is characterized with an angiocentric and angiodestructive pattern of growth with associated geographical necrosis and ulceration. And coagulative necrosis and apoptotic bodies are frequently countered. The immunophenotype of NK/T lymphoma cells is positive for CD2, CD56, cytoplasmic CD3 epsilon (ε) while it is negative for surface CD3 [4]. Due to its rarity and unique characteristics, most data concerning extranodal NK/T-cell lymphoma, nasal type was derived from small case series or retrospective analyses. And not a single standard treatment method has been proposed yet. NK/T-cell lymphoma is usually presented with localized extranodal disease, and local radiation therapy (RT) alone has been the most popular treatment modality [5]. The relapse rate after local RT alone is very high, and local recurrence is the most frequent failure pattern [6]. So RT alone is suboptimal because of the high rate of local or systemic failure. It has been reported that three or four cycles of cyclophosphamide, adriamycin, oncovin, prednisone (CHOP) followed by involved field RT (IF RT) is superior to eight cycles of CHOP alone [7]. CHOP or CHOP-like regimens, which has been generally accepted as the standard regimen for aggressive NHL such as ENKTL [8], was generally utilized in most countries for patients with

Table 1. Patients characteristics

Characteristic	Group A	Group B
Total number of patients (n)	30	34
Age (years)		
Median	44	46
Range	21-68	22-73
≥ 60	8	10
< 60	22	24
Gender		
Male/Female	19/11	24/10
Stage I/II	18/12	22/12
B symptom (+)	13	18
Lactate dehydrogenase > normal	11	12
Performance status (ECOG)		
0	6	7
1	20	23
2	3	3
3	1	1
International Prognostic Index		
0	11	13
1	12	14
2	5	3
3	2	4
Sites of paranasal extension		
Ethmoid sinus	8	10
Maxillary sinus	7	8
Nasopharynx	5	6
Hard palate	6	4
Soft palate	1	4
Local skin	3	2

ENKTL for decades [9]. However, owing to its relatively low response rate, more and more novel regimens have emerged with promising results, especially L-asparaginase-based regimens [10]. In this study the treatment outcomes of four cycles of CHOP or gemcitabine, dexamethasone, L-asparaginase (GDL) followed by IF RT for treatment of stage I-II non-bulky nasal NK/T-cell lymphoma was analyzed.

Materials and methods

Patient selection

From January 2010 to October 2014, 64 patients with newly diagnosed extranodal NK/T-cell lymphoma, nasal type were randomly divided into two groups in Oncology Department of the Affiliated Hospital of Qingdao University. The characteristics of these patients were summarized in **Table 1**. The median age was 44 (range 21-72). The stage was based on 1989 Ann Arbor-Cotwolds staging system, which included thorough history take and physical examination, B ultrasonic examination, routine blood and urine tests, computed tomography (CT) scans of head and neck, abdomen and pelvis. None of the patients received any treatment before. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Qingdao University. Written informed consent was obtained from all participants.

Treatment

Group A (n = 30) received four cycles of CHOP while group B (n = 34) received four cycles of GDL, after the chemotherapy both of the groups received IF RT. The CHOP regimen consists of cyclophosphamide, 750 mg/m^2, iv, day 1; adriamycin, 50 mg/m^2, iv, day 1; oncovin, 1.4 mg/m^2 (maximum dose of 2 mg per cycle) iv, day 1 and prednisone, 100 mg/d, po days 1-5. The GDL regimen is consisted of gemcitabine, 1000 mg/m^2, iv, days 1 and 8; dexamethasone, 10 mg/m^2, iv, days 1-5; and L-asparaginase, 5000 u/m^2, iv, days 1-7. The chemotherapy cycles were repeated at twenty-one days intervals. IF RT began three weeks after four cycles of chemotherapy. The total radiotherapy dose was 45 Gy or 50 Gy administered over five weeks by conventional fractionation schedule (1.8 or 2.0 Gy/fraction, five fractions/week) to the prechemotherapy gross disease extent.

Response and safety assessments

Tumor response was assessed after every 2 cycles of chemotherapy or before and after IF RT on the basis of standardized response criteria for non-Hodgkin lymphoma [11]. All adverse effects after chemotherapy were graded based on version 3.0 of National Cancer Institute Common Terminology Criteria of Adverse Events. PFS was calculated from the date treatment began to the date when disease progression or relapse. Overall survival duration was measured from the date of diagnosis to the date of death or the last follow-up visit.

Statistical analysis

Statistical analysis was performed using SPSS Software Package Version 17.0 (SPSS Inc., Chicago, IL, USA). Data were expressed as mean ±

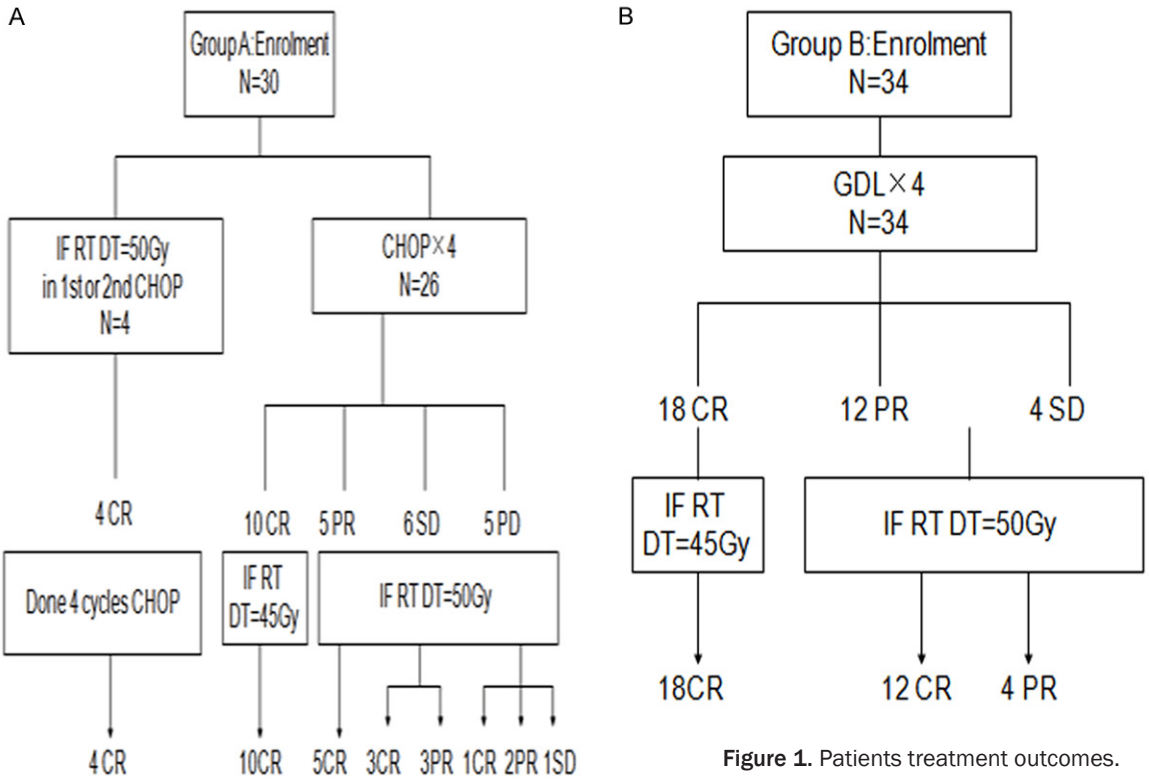

Figure 1. Patients treatment outcomes.

standard deviation or proportions, as appropriate. Remission rates and the differences in toxicity between the two groups were compared by using chi-square test. The progression free survival (PFS) and overall survival (OS) rates were calculated by the Kaplan-Meier method. Survival curves were compared by statistical differences using the log-rank test in univariate analysis. All *P* values reported were two-sided, and a probability level of less than 0.05 was considered statistically significant.

Results

Treatment response

Group A: Four patients received radiation during the first or second cycle of CHOP, because of bleeding from the primary tumour site. They all achieved CR. For the remaining 26 patients, after 4 cycles of CHOP, 10 (33.3%) and 5 (16.7%) patients achieved CR and PR, respectively, which meant the response rate was 50%. IF RT was delivered as scheduled following chemotherapy to all of the remaining 26 patients. After IF RT, 23 of 30 patients (76.7%) achieved CR and 5 of 30 patients (16.7%) achieved PR. The treatment results are shown in **Figure 1A** and **1B**.

Group B: All of the 34 patients received 4 cycles of GDL. There were 18 (52.9%) and 12 (35.3%) patients achieved CR and PR, respectively. IF RT was delivered as scheduled following chemotherapy in all of 34 patients. After IF RT, 30 of 34 patients (88.2%) achieved CR and 4 patients (11.8%) achieved PR.

Before the IF RT the response rate was 50% versus 88.2% ($P = 0.001$) and the CR rate was 33.3% versus 52.9% ($P = 0.115$) between Group A and B. After the IF RT was completed, the response rate was 93.3% versus 100% ($P = 0.216$) and the CR rate was 76.7% versus 88.2% ($P = 0.221$) in group A and B, respectively.

Progression free survival and overall survival rate

After a median follow up of 29.5 (range 11-48) months for survivors, the median PFS was 37.523 (95% CI: 31.322-43.724) months and 40.702 (95% CI: 35.473-45.932) months for group A and B, respectively (log-rank test, $P = 0.401$; **Figure 2A**), and the estimated three years progression free survival (PFS) rate was 51% versus 64%. Median overall survival (OS) was 37.255 (95% CI: 30.874-43.635) months

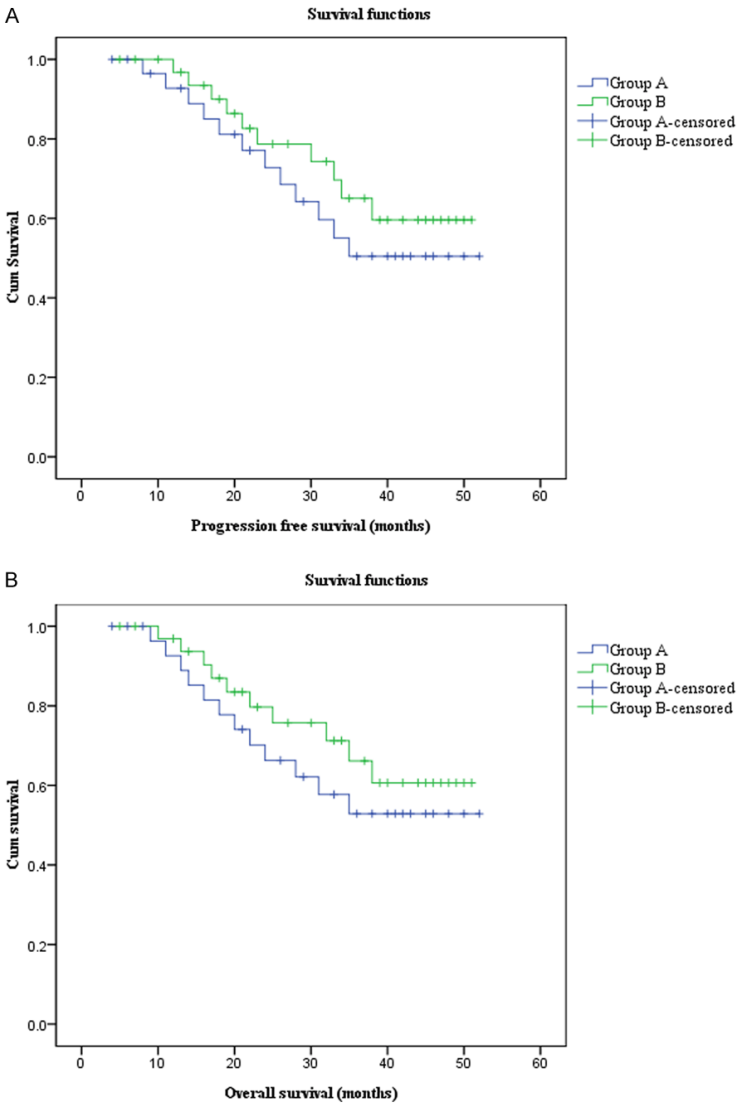

Figure 2. The PFS and OS of patients. A: The PFS of patients (log-rank test, $P = 0.401$); B: The OS of patients (log-rank test, $P = 0.402$).

and 40.558 (95% CI: 35.212-45.903) months for group A and B, respectively (log-rank test, $P = 0.402$; **Figure 2B**), and the estimated three years overall survival (OS) was rate was 53% versus 66%.

Treatment toxicity

The main adverse events were shown in **Table 2**. L-asparaginase and gemcitabine were generally well tolerated, and all of the group B patients completed the treatment. Major adverse effects were myelosuppression, gastrointestinal reactions, thrombosis, lack of power, insomnia, and blood glucose fluctuation. According to WHO hematologic toxicity evaluation criterion, fewer grade 3-4 were observed. Totally grade 1-2 neutropenia was found in 20 (58.8%) patients and grade 1-2 thrombocytopenia was observed in 20 (58.8%) patients. The non-hematologic toxicity was nausea, vomiting and constipation. And there was no significant difference in hematologic or nonhematologic toxicity between group A and B (chi-square test or fisher's exact test if needed). It is worth mentioning that two patients experienced anaphylactic reactions during L-asparaginase infusion. And there was no diabetes or pancreatitis occurred.

Discussion

In this prospective study, it was found that treatment with L-asparaginase-based chemotherapy for extranodal NK/T-cell lymphoma, nasal type was much more efficient compared to classical CHOP. Extranodal NK/T-cell lymphoma, nasal type, as a relatively uncommon subtype of non-Hodgkin's lymphoma, frequently occurs in middle aged men, and usually presents as a localized disease involving the head and neck. Furthermore, patients always show good performance status [6, 7]. However, the overall prognosis of the disease is poor because of frequent relapse or resistance to treatment [12]. And nowadays most data concerning extranodal NK/T-cell lymphoma, nasal type available are from small case series or retrospective analyses. No single standard treatment method has been proposed yet.

For stage I/II nasal type extranodal NK/T-cell lymphoma, radiotherapy is an important treatment method. The response rate of radiotherapy alone was 60%-80%, and CR rate was 40%-80% [13]. Despite the excellent initial response to radiotherapy alone, a high relapse rate of

Table 2. Treatment toxicity

WHO grade	1		2		3		4	
	A	B	A	B	A	B	A	B
Hematologic								
Neutropenia	2	3	20	18	5	8	3	5
Thrombocytopenia	3	5	18	20	7	5	2	4
Anemia	10	12	12	19	6	2	2	1
Nonhematologic								
Nausea, vomiting	3	5	10	13	12	15	5	1
Hepatic	13	14	8	12	5	4	4	4
Renal	20	15	6	13	3	4	1	2
Peripheral nerves	14	10	8	16	6	6	2	2

WHO, world health organization; A, group A; B, group B.

44%-50% was reported [13-15]. Including involved field and margin failures, the local failure usually occurs within the first year. Ko et al report that systemic and local relapse rate of patients with early stage nasal type extranodal NK/T-cell lymphoma who received radiotherapy alone were 25% and 10%, respectively [16]. In light of the high relapse rate with radiotherapy alone, combination of chemotherapy and radiotherapy becomes the current standard of care in patients who can tolerate systemic treatment [13, 17]. And for the early stage nasal type extranodal NK/T-cell lymphoma, radiotherapy alone is not enough. Chemotherapy has become one of the mainstay of treatment for the NK/T-cell lymphoma. Conventional CHOP or CHOP-like regimens show unsatisfied outcome, with CR rate less than 20% [18]. And there is a high rate of disease progression (30-40%) and relapse after initial CR (30-40%) [13, 18, 19].

The unsatisfactory result of CHOP may be due to expression of the multi-drug resistance (MDR) gene and high levels of P-glycoprotein (P-gp) in NK/T-cell lymphoma cells which underlies the resistance to anthracyclines and vinca alkaloids [13, 18, 20]. The high level of functional P-gp expression is considered to contribute to the chemotherapy resistance of NK/T-cell lymphoma [20, 21]. Yamaguchi et al found 9 of the 10 patients were P-gp positive [20]. One of the ways to circumvent the chemotherapy resistance is to use anti-cancer agents that are not influenceded by P-gp. Regimens based on non-P-glycoprotein efflux chemotherapeutic agents such as L-asparaginase may actually be more effective in these patients. Recently some studies showed that NK/T-cell lymphoma treated with L-asparaginase-base regimen acquired the favourable outcome [22, 23].

Owing to that some NK/T-cell lymphoma cells are unable to synthesize L-asparagine, they die when stores of L-asparagine are depleted by L-asparaginase [24]. So L-asparaginase may become a possible agent for a new chemotherapy regimen for NK/T-cell lymphoma. L-asparaginase hydrolyzes serum L-asparagine and deprives some cells of the required amino acid to yield anticancer effects in certain tumor cells, especially in lymphoma cells which lack L-asparagine synthetase [24, 25]. Whereas, the normal cells which contain a large number of L-asparagine synthetase are able to synthesize L-asparagine needed by themselves. Taking advantage of complementary DNA microarrays, Scherf reported a moderately high negative correlation (-0.44) between L-asparagine synthetase messenger RNA expression and L-asparaginase sensitivity in 60 lymphoma cell lines [26].

Gemcitabine is a novel nucleoside analogue with proven activity in solid tumors and NHL. It acts as a competitive substrate with deoxycytidine for incorporation into DNA, thus inhibiting DNA replication and repair. Although gemcitabine is similar to Ara-C in structure, its cellular pharmacology and mechanism of action differs remarkably [27, 28]. And it would not be affected by the MDR phenotype [25]. Gemcitabine has proven to be effective in untreated patients with T-cell lymphoma as a single agent. Moreover, its modest toxicity profile and easy schedule of administration make it an ideal agent for frontline use [28].

In conclusion, although this study showed that different chemotherapy combined with radiotherapy did not improve the survival of patients with early stage extranodal NK/T-cell lymphoma, the regimens of GDL have greatly improved the response rate and quality of life compared with the CHOP. Since the relapse rate after local RT alone is very high, chemoradiotherapy is necessary to NK/T-cell lymphoma. Data from our study showed that the first line combination of GDL with radiotherapy to treat early stage extranodal NK/T-cell lymphoma was effective and sage, which might provide clinical evidence

for early stage extranodal NK/T-cell lymphoma treatment. However, as extranodal NK/T-cell lymphoma, nasal type is a rare disease and the sample size of our study was small, further study to demonstrate the results was needed.

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Disclosure of conflict of interest

None.

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