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ORIGINAL ARTICLE

Three-dimensional conformal radiotherapy plus concurrent DICE chemotherapy for early-stage nasal-type natural killer/T-cell lymphoma of Waldeyer's ring: A single-institution study*

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Abstract

Objective Nasal-type natural killer/T-cell lymphoma of Waldeyer's ring (WR-NK/TL) has different clinicopathological characteristics from those of other subtypes of NK/T lymphoma; thus, the optimal treatment remains unclear. To find a more effective treatment model for WR-NK/TL, we conducted a single-center study of concurrent radiochemotherapy.

Methods Forty-five patients with newly diagnosed stage IE to IIE WR-NKTL were randomly divided into two groups. The 23 cases in the concurrent radiochemotherapy group were treated with three-dimensional conformal radiotherapy (48–52 Gy) and 2 courses of DICE (dexamethasone, ifosfamide, cisplatin, and etoposide) synchronous chemotherapy. The 22 cases in the radiotherapy group only received three-dimensional conformal radiotherapy (50–54 Gy). The primary end points were overall survival (OS), progression-free survival (PFS), and toxicity.

Results The 1-, 3-, and 4-year OS and PFS rates were 95.5%, 65.6%, and 45.9%, and 86.4%, 56.0%, and 46.7% in the radiotherapy group, and 100%, 88.5%, and 88.5%, and 100%, 82.0%, and 73.8% in the concurrent radiochemotherapy group, respectively. The OS (P = 0.0477) and PFS rates (P = 0.0488) were higher in the concurrent radiochemotherapy group than in the radiotherapy group. The overall response rate was 100% in both the radiotherapy group [complete response (CR), 18 cases] and concurrent radiochemotherapy group (CR, 22 cases). The concurrent radiochemotherapy group had more severe side effects, especially grade 3 + 4 events, such as leukopenia, anorexia, and stomatitis. However, side effects benefiting from excellent oral care were endurable.

Conclusion Radiotherapy plus concurrent DICE chemotherapy may be an effective and safe comprehensive treatment for patients with WR-NKTL.

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Key words: nasal cavity; NK/T-cell lymphoma; prognosis; radiotherapy; chemotherapy

The clinical features and biological behaviors for nasal-type natural killer/T-cell lymphoma of Waldeyer's ring (WR-NKTL) are distinct from other types of lymphoma. This disease is positively correlated with the Epstein-Barr virus (EBV), so there are some specific differences in treatment and prognosis. Due to its rarity and lack of prospective clinical trials, the optimal therapy needs to be clearly defined. Radiotherapy has been established as the primary curative therapy for NKTL [1–2], but the treatment failure rate is high due to distant extranodal dissemination and lymph node involvement [1].

Chemotherapy, which is systemically administered, has obvious curative effects on decreasing the rate of distant metastases in some malignant tumors [3–4]. However, the effect of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy for NKTL remains controversial, some researchers think that chemotherapy could not improve prognosis and prolong long-term sur-

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vival time [5]. A study showed that the DICE (dexamethasone, ifosfamide, cisplatin, and etoposide) regimen, which comprised multidrug resistance-nonrelated agents, could improve the prognosis of lymphoma refractory to CHOP chemotherapy [6]. Indeed, the EBV viral load in tumor tissue is also an important prognostic factor of ENKTL [7]. Interestingly, etoposide is effective against EBV-associated hemophagocytic syndrome [8]. More importantly, concurrent radiochemotherapy addresses both local-regional and distant disease simultaneously, and has been defined as a standard therapy for some solid tumors [9–10].

To investigate a more effective treatment of WR-NKTL, we selected three-dimensional conformal radiotherapy (3-DCRT) plus DICE concurrent chemotherapy to treat the patients with WR-NKTL, in comparison with 3-DCRT alone.

Patients and methods

Eligibility criteria of patients

To be eligible, patients were required to have a biopsy-proven diagnosis of WR-NKTL, to be 15 to 65 years old, to have at least one measurable disease, and to have disease classified as Ann Arbor stage IE or IIE. Other eligibility criteria included no prior radiotherapy or chemotherapy, and performance status of 0 to 2 according to the Eastern Cooperative Oncology Group (ECOG) scale.

Patients with adequate hematologic function [i.e., white blood cell (WBC) count ≥ 4000 /μL, hemoglobin level ≥ 10.0 g/dL, and platelet count ≥ 100 000 /μL], renal function (i.e., serum creatinine level ≤ 1.5 mg/dL and creatinine clearance ≥ 50 mL/min), and hepatic function (i.e., aspartate aminotransferase and alanine aminotransferase levels ≤ 4 times the normal upper limit, total bilirubin level ≤ 2.0 mg/dL), and normal electrocardiographic result.

Diagnosis of WR-NKTL was based on the presence of histological features and immunophenotypes compatible with NK/T-cell lymphoma (e.g., cytoplasmic CD3+, CD3ε+, CD20–, CD56+, positive for cytotoxic molecules, and positive for EBV by fluorescence *in situ* hybridization). The tumor primary site and size were assessed by using magnetic resonance imaging, computed tomography, and nasopharyngoscopy.

The exclusion criteria were as follows: patients with prior concomitant malignant tumors and any coexisting medical problems of sufficient severity to prevent full compliance with the study protocol, patients with nasal cavity natural killer/T-cell lymphoma and local recurrence of WR-NKTL, patients with WR-NKTL with treatment history (including chemotherapy and/or radiotherapy), and patients with ECOG performance scale scores ≥ 3.

All the patients were informed and voluntarily participated. The study was approved by the Institutional Review Board of the Affiliated Hospital of North Sichuan Medical College, Sichuan Province, China.

Radiotherapy

All the patients were treated with three-dimensional conformal radiotherapy delivered with a 6-MV linear accelerator. Radiotherapy was divided into two courses. In the first course, the prescription was 40 Gy in 200-cGy fractions, given a 95% isodose planning target volume (PTV). Clinical target volume (CTV) included gross tumor volume (GTV) of the nasopharynx, oropharynx, hypopharynx, lymphatic drainage regions of the parapharyngeal space, and middle and upper neck regions. PTV included CTV with a 5-mm margin. In the late course, the total dose of prescription increased to 48–54 Gy given clinical target volume one (CTV1). CTV1 included GTV with at least a 15- to 20-mm margin on the second computed tomography.

Normal organs contouring included lens, eyeball, optic nerve, optic chiasm, pituitary, oral cavity, parotid, and cervical spinal cord. The definition of dose limit for normal organs was according to the standard of reference 1 [1]. The bilateral lower neck and supraclavicular areas were treated through an anterior field, with a prevention dose of 46 Gy and the lymph node dose added until 54 Gy through the involved field radiotherapy.

Chemotherapy

The chemotherapy regimen used was DICE (dexamethasone, 10 mg, i.v., q6h, d1–4; ifosfamide, 1 g/m^2/d, i.v., d1–4; mesna for detoxification; cisplatin, 25 mg/m^2/d, i.v., d1–4; etoposide, 100 mg/m^2/d, i.v., d1–4, q4w), which was administered in the first and fourth weeks of radiotherapy simultaneously. On the second day after the end of chemotherapy, the recombinant human granulocyte colony-stimulating factor was routinely used for preventing decreased WBC count for 3 to 5 days.

Statistical analysis

The primary end points were overall survival (OS), progression-free survival (PFS), and toxicity. OS was measured from the date of enrollment to the date of death from any cause and censored at the date of the last follow-up visit. PFS was defined as the time from the date of enrollment to the date of documented disease progression and censored at the date of the last follow-up visit. Toxicity was evaluated according to the National Cancer Institute Common Terminology Criteria of Adverse Events version 3.0. The secondary end point was the response rate, which was calculated as the proportion of patients classified as having complete and partial responses. Treatment response was assessed according to the World Health Organization criteria.

Table 1 Clinical characteristics between two groups (*n*)

	RT (22)	CCRT (23)	χ^2	*P*
Gender				
Male	16	15	0.2959	0.5865
Female	6	8		
Age (years)				
≤ 60	20	19	20	0.2511*
> 60	2	4		
Ann Arbor stage				
I E	13	14	0.0148	0.9031
II E	9	9		
Elevated LDH level	4	5	4	0.2778*
B group symptoms	5	6	0.0687	0.7932
Neck lymph node involvement	14	13	0.2372	0.6263
ECOG score				
0	5	4	0.5401	0.7634
1	11	14		
2	6	5		
Stage-modified IPI [11]				
0	5	6	0.1933	0.9079
1	10	11		
2	7	6		
Primary site				
Nasopharynx	14	15	0.4291	0.8069**
Tonsil	7	6		
Tongue root	1	2		

Note: RT, radiotherapy group; CCRT, concurrent radiochemotherapy group; LDH, lactic dehydrogenase; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index. * Fisher's exact test; ** Likelihood ratio chi-square test

Both OS and PFS were calculated by using the Kaplan-Meier method. The survival curves between the different groups were compared by using the log-rank test. A chi-square analysis was performed for qualitative data comparison. All analyses were performed by using the SAS version 8.0.

Results

Patient characteristics

Forty-five patients enrolled from January 2008 to December 2012 were randomly divided into two groups (radiotherapy group, 22 cases; concurrent radiochemotherapy group, 23 cases). The patient clinical characteristics of both groups listed and compared in Table 1 were assessed by experienced professional diagnostic radiologists and radiation oncologists. The median age was 41 years (range, 15–65 years).

Response to treatment and survival

The overall response to treatment was 100% in the two groups, respectively. The complete and partial response rates were respectively 81.8% (18/22) and 18.2% (4/22) in the radiotherapy group, and 95.7% (22/23) and 4.3% (1/23) in the concurrent radiochemotherapy group. No significant difference in complete response was observed between the two groups ($F = 22$, $P = 0.1377$).

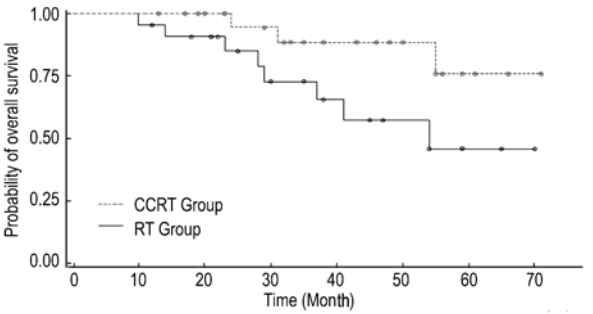

Fig. 1 Overall survival (OS) for two groups. The OS rate in concurrent radiochemotherapy (CCRT) group was higher than that in radiotherapy (RT) group

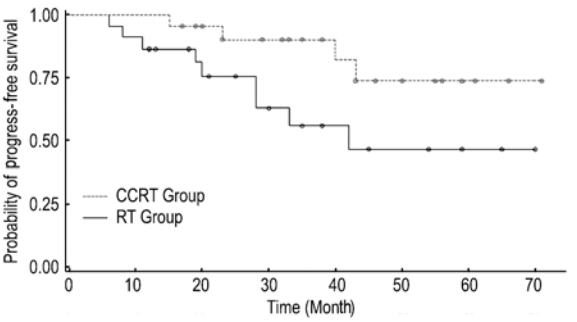

Fig. 2 Progression-free survival (PFS) for two groups. The PFS rate was higher in concurrent radiochemotherapy (CCRT) group than in radiotherapy (RT) group

With a median follow-up time of 35 months, the 1-, 3-, and 4-year OS and PFS rates were 95.5%, 65.6%, and 45.9%, and 86.4%, 56.0%, and 46.7%, respectively, in the radiotherapy group, but were 100%, 88.5%, and 88.5%, and 100%, 82.0%, and 73.8% in the concurrent radiochemotherapy group, indicating a significant difference in OS rate ($\chi^2 = 3.9213$, $P = 0.0477$) and PFS rate ($\chi^2 = 3.8837$, $P = 0.0488$; Fig. 1 and 2).

Toxicity

Some cases of toxicity were more severe in the concurrent radiochemotherapy group than in the radiotherapy group (Table 2), and the differences of the two groups in grade 3 + 4 leucopenia, anorexia, and stomatitis were statistically and clinically significant. Notably, in the concurrent radiochemotherapy group, 11 patients who experienced grade 3 + 4 stomatitis had more severe nausea and anorexia, suggesting the importance of strengthening oral care. For the patients, we prescribed 10-mL mixed liquor (ingredients: 20% mannitol, 250 mL; gentamicin,

Table 2 Toxicity profiles between two groups

Toxicity	RT group (22)				CCRT group (23)				χ^2	*P*
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4		
Leukopenia	3	6	1		2	3	7	1	21	0.0122**
Thrombocytopenia	2				2	4			2	0.1082*
Anemia	3	2			2	4	2		0.7955	0.3724
Nausea	6	7	1		3	5	4		1	0.1595*
Vomit	3	5	1		3	6	5		1.7929	0.1806
Diarrhea	2	1			4	2	1		1.8358	0.1754
Anorexia	11	9	1		6	8	9		1	0.0056**
Constipation	5	3	2		4	7	2		0.5512	0.4578
Stomatitis	9	9	3	1	5	7	9	2	4.4466	0.0350**
Neuropathy	5				4	4			0.7955	0.3724

Note: RT, radiotherapy group; CCRT, concurrent radiochemotherapy group. * Fisher's exact test; ** based on grade 3 + 4 events

Table 3 Analysis of treatment failure between 2 groups (*n*)

Progress parts	RT (22)	CCRT (23)
Local recurrence	2	1
Lymph node involvement	3	1
Extra-nodal dissemination		
Lung	3	1
Skin	1	
Bone	2	1

Note: RT, radiotherapy group; CCRT, concurrent radiochemotherapy group

6.4×10^5 U; dexamethasone, 20 mg) three times a day slowly with the aim of relieving the physical inflammatory reaction and then to infiltrate the mouth cavity by using the mixed liquor (ingredient: interleukin-11, 2 mg; normal saline, 100 mL) to promote oral mucosa cell repair and growth.

Treatment failure analysis

The pattern of failure was shown in Table 3. During the follow-up period, 13 of 45 patients experienced disease progression. The failure rate was 23% higher in the radiotherapy group than in the concurrent radiochemotherapy group but did not significantly differ between the groups [40.9% (9 of 22) vs. 17.4% (4 of 23); $P = 0.0819$]. Furthermore, extra-nodal dissemination and lymph node involvement were the primary failure patterns. In the patients who experienced disease progression in the radiotherapy group, the sites of failure were observed in the local region alone ($n = 1$), lymph node alone ($n = 2$), lung alone ($n = 2$), bone alone ($n = 2$), lung plus lymph node plus local region ($n = 1$), and skin ($n = 1$). In the concurrent radiochemotherapy group, the sites of failure were observed in the local region ($n = 1$), lymph node ($n = 1$), lung ($n = 1$), and bone ($n = 1$), respectively.

Discussion

This is the first study to our knowledge to administrate concurrent radiochemotherapy for WR-NKTL, and our comprehensive treatment was significantly different from those of previous studies for NKTL [11–12].

We analyzed the treatment response between the concurrent radiochemotherapy and radiotherapy groups. OS and PFS rates were better in the concurrent radiochemotherapy group than in the radiotherapy group, with significant difference. Similar to the results of single-agent cisplatin concurrent radiochemotherapy combined with DICE chemotherapy, the response rate, 3-year OS rate, and 3-year PFS rate were 100%, 86.28%, and 85.19%, respectively [11]. Our treatment response was superior to the 2-year OS rate of 78% and PFS rate of 67% as reported by Yamaguchi and colleagues [12], and superior to the historical control (45%) [13]. Li and colleagues [1] reported that the 5-year OS and PFS rates of radiotherapy combined with chemotherapy were 75% and 65%, while that of chemotherapy alone were 52% and 34%, respectively. The combination chemotherapy achieved better effect, showing that radiotherapy combined with chemotherapy can improve the long-term survival of patients with NK/T cell lymphoma in the Waldeyer's ring region [1], which was consistent with the conclusion of our study. We consider concurrent radiochemotherapy to be more effective than radiotherapy alone for the treatment of nasal-type natural killer/T-cell lymphoma in Waldeyer's ring. Several reasons should be considered: First, three-dimensional conformal radiotherapy can further improve the local control rate than that of conventional radiotherapy [14]. Second, DICE chemotherapy replaced CHOP to avoid the multidrug resistance that is caused by P-glycoprotein expressed in tumor cells and poor outcome of CHOP chemotherapy for natural killer/T-cell lymphoma [15]. In our study, patients who received radiotherapy alone had a high failure rate compared with those who received

concurrent radiochemotherapy. However, the failure rate in the concurrent radiochemotherapy group was lower than that in the radiotherapy alone. This suggests that concurrent chemotherapy can significantly decrease the occurrence rate of failure of distant extranodal dissemination and lymph node involvement, thus improving long-term survival. Finally, concurrent radiochemotherapy can improve anticancer efficacy [10].

The toxicity profile of concurrent radiochemotherapy for WR-NKTL has not been well established. In a phase II study of concurrent radiochemotherapy for newly diagnosed local natural killer/T-cell lymphoma, the hematologic toxicity was minimal during radiochemotherapy [9]. However, notably, this study used cisplatin alone in combination with radiotherapy, which was different with our chemotherapeutic regimen. Our data indicated that infection and hematologic toxicity were common and severe. Furthermore, all of the patients who benefitted from the excellent oral care completed the treatment successfully.

The limitations of our study include the small sample size and single-center study. Furthermore, limited treatment is also our shortage. Considering the poor prognosis to some patients after treatment, it is possible that high-dose chemotherapy and hematopoietic stem-cell transplantation with autologous or allogeneic hematopoietic stem cells may be beneficial to selected patients [16–17].

In summary, our study suggests that concurrent radiochemotherapy has possible therapeutic potential in the treatment of WR-NKTL. Further studies are needed to test the efficiency of this treatment by means of a multicenter, randomized, large-scale study to evaluate the possible prognosis before therapy and to selectively administer individual therapy such as hematopoietic stem cells, with the aim of promoting the long-term survival of patients with nasal-type natural killer/T-cell lymphoma of Waldeyer's ring.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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