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**CLINICAL INVESTIGATION** **Lymphoma**

# SALVAGE TREATMENT IMPROVED SURVIVAL OF PATIENTS WITH RELAPSED EXTRANODAL NATURAL KILLER/T-CELL LYMPHOMA, NASAL TYPE

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**Purpose: To evaluate the clinical outcome of salvage treatment for patients with relapsed natural killer (NK)/T-cell lymphoma, nasal type.**

**Methods and Materials: Forty-four patients who had achieved complete response during initial treatment and experienced histologically proven relapse were reviewed. Twenty-nine of them received salvage treatment with radiotherapy (RT) alone ($n$ = 7), chemotherapy (CT) alone ($n$ = 10), or both RT and CT ($n$ = 12); the other 15 patients received best supportive care alone.**

**Results: The estimated 5-year overall survival (OS) rate for patients with or without salvage treatment was 37.8% vs. 0 ($p < 0.0001$), respectively. Salvage CT did not improve survival of relapsed Stage IE and IIE patients. Among relapsed Stage IIIE and IVE patients who received salvage treatment, RT developed significantly better survival when compared with that of non-RT (1-year OS, 62.5% vs. 0, $p = 0.006$). Relapsed Ann Arbor stage and receiving salvage treatment were found to be significant factors influencing OS at both univariate and multivariate levels.**

**Conclusions: Salvage treatment improved survival in patients with relapsed NK/T-cell lymphoma, nasal type. Salvage RT may play an important role in salvage treatment of relapsed extranodal NK/T-cell lymphoma.**


**Extranodal NK/T-cell lymphoma, Salvage treatment, Retrospective analysis.**

## INTRODUCTION

Extranodal natural killer (NK)/T-cell lymphoma, nasal type is a recently recognized distinct entity within the World Health Organization classification of lymphoma (1). This tumor was previously known as lethal midline malignant reticulosis, polymorphic malignant reticulosis, or angiocentric immunoproliferative lesion. The most frequent immunophenotype is CD2+, CD3−, cytoplasmic CD3$\varepsilon$+, and CD56+, and it is usually positive for Epstein-Barr virus by *in situ* hybridization (1, 2). The most common sites of involvement are nasal cavity, nasopharynx, and palate. It is much more common in Asia and Latin America than in Europe and North America—approximately 2.6–10.7% of cases of non-Hodgkin's lymphoma and 40–74% of all nasal and nasopharyngeal lymphomas in Asia (2–5).

Previous studies demonstrated that the 5-year overall survival (OS) rate for NK/T-cell lymphoma, nasal type is <41% (3), and the majority of the progression, which is known as locoregional and distant relapse, occurred within 2 years. Although the relapse rate ranged from 25% to 61% in several studies (2, 3, 5–8), the survival and prognosis of relapsed NK/T-cell lymphoma, nasal type is rarely mentioned, and the salvage strategies have not yet been defined. Therefore, we conducted this retrospective study to evaluate the clinical

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outcome of salvage treatment for patients with relapsed NK/T-cell lymphoma, nasal type, and prognostic factors were also analyzed.

## METHODS AND MATERIALS

### *Patient eligibility and evaluation*

From May 1997 to January 2005, 47 patients who had been diagnosed with polymorphic malignant reticulosis or NK/T-cell lymphoma and who had achieved complete response presented with relapse at the Cancer Center, West China Hospital, Sichuan University, Chengdu, and the Department of Radiochemotherapy, Zhongnan Hospital, Wuhan University, Hubei, China. All these patients were initial Stage IE–IIE. Biopsies were carried out for all patients to confirm diagnosis and relapse. An experienced pathologist reviewed all the histologic sections. Immunohistochemical examinations were performed to affirm pathologic diagnosis, and Epstein-Barr virus *in situ* hybridization was performed in CD56− cases. Forty-four patients were included in our analysis. All the histopathologic findings showed angiocentricity, necrosis, and pleomorphic infiltration. Twenty-seven patients were CD20−, CD56+, CD3$\varepsilon$+, or CD45RO+ and TIA-1+ or granzyme B+, and 17 patients exhibited CD20−, CD56−, Epstein-Barr virus *in situ* hybridization positive, CD3$\varepsilon$+ or CD45RO+, and TIA-1+ or granzyme B+. Three patients were excluded for having other types of lymphoma. All patients underwent physical examinations, complete blood count, serum lactate dehydrogenase (LDH) evaluation, screening blood tests of renal and hepatic function, nasal panendoscopies, computed tomography scan of head, neck, chest, abdomen, and pelvis, and bone marrow biopsies for staging their disease. Patients were restaged according to the Ann Arbor staging system.

### *Treatment*

Of all 44 patients included in the analysis, 10 were treated with salvage chemotherapy (CT) alone, 7 patients received salvage radiotherapy (RT) alone, and 12 patients were given combined-modality treatment of CT and RT (CMT) after diagnosis of relapse; 15 patients received no treatment except best supportive care (BSC) without palliative CT or RT. Of these 15 patients, 3 did not receive salvage treatment for their poor performance status, and 12 patients refused salvage treatment. Among 22 patients with salvage CT, 16 were treated with a CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen and 6 with an EPOCH (etoposide, cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen. They received one to four cycles of CT, and the median number of cycles of salvage CT was two. Treatment details of the 29 patients receiving salvage treatment are described in Table 1.

Salvage RT was designed by a three-dimensional conformal radiotherapy (3D-CRT) treatment-planning system. The RT was delivered using 6-MV photon beams in daily fractions of 2.0 Gy, 5 days per week, for a total dose of 30–60 Gy (median dose, 40 Gy). The clinical target volume covered all involved areas, with adequate margins.

### *Definition and statistical analysis*

Complete response (CR) was defined as complete regression of symptoms, signs, and radiographic disease. Relapse time was measured from the date of achieving CR during the initial treatment to the time of the first local or distant relapse. Overall survival was calculated from the date of first relapse to death or last follow-up. Overall survival was estimated by the Kaplan-Meier method. In univariate analysis, survival curves were compared by the log–rank test. Prognostic factors included age, gender, relapsed Ann Arbor stage, CD56, Eastern Cooperative Oncology Group performance status score (ECOG score), LDH, B symptom, International Prognostic Index (IPI) score, relapse time, and receiving salvage treatment or not. Multivariate analysis was carried out using the Cox regression model. Comparisons of qualitative data were done by $\chi^2$ test or Fisher's exact test. All these statistical analyses were performed with SPSS 13.0 (SPSS, Chicago, IL).

Table 1. Treatment characteristics of individual patients receiving salvage treatment

| Patient ID | Stage | Salvage RT dose (Gy) | CT regimen (no. of cycles) | Survival time (month) | Alive (Y) or not (N) |
|---|---|---|---|---|---|
| 1 | IBE | 44 | CHOP (2) | 12 | Y |
| 2 | IBE | 0 | CHOP (2) | 6 | Y |
| 3 | IBE | 36 | Nil | 7 | N |
| 4 | IBE | 40 | CHOP (2) | 14 | Y |
| 5 | IBE | 40 | Nil | 18 | Y |
| 6 | IAE | 40 | Nil | 24 | Y |
| 7 | IAE | 40 | CHOP (2) | 24 | N |
| 8 | IBE | 40 | Nil | 38 | Y |
| 9 | IAE | 44 | CHOP (4) | 48 | Y |
| 10 | IAE | 30 | Nil | 108 | Y |
| 11 | IIAE | 0 | CHOP (3) | 6 | N |
| 12 | IIAE | 0 | EPOCH (4) | 11 | N |
| 13 | IIAE | 60 | CHOP (3) | 24 | N |
| 14 | IIAE | 46 | CHOP (4) | 35 | Y |
| 15 | IIAE | 44 | Nil | 50 | Y |
| 16 | IIBE | 44 | Nil | 64 | Y |
| 17 | IIIAE | 46 | CHOP (2) | 3 | N |
| 18 | IIIAE | 0 | CHOP (2) | 5 | N |
| 19 | IVAE | 0 | CHOP (1) | 1 | N |
| 20 | IVAE | 40 | EPOCH (3) | 6 | Y |
| 21 | IVBE | 0 | CHOP (1) | 2 | N |
| 22 | IVAE | 0 | EPOCH (1) | 3 | N |
| 23 | IVAE | 0 | CHOP (2) | 4 | N |
| 24 | IVBE | 0 | CHOP (2) | 4 | N |
| 25 | IVBE | 0 | EPOCH (3) | 5 | N |
| 26 | IVBE | 40 | EPOCH (3) | 12 | N |
| 27 | IVAE | 56 | CHOP (2) | 17 | N |
| 28 | IVBE | 50 | EPOCH (3) | 17 | N |
| 29 | IVAE | 40 | CHOP (2) | 20 | Y |

*Abbreviations:* RT = radiotherapy; CT = chemotherapy; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; EPOCH = etoposide, cyclophosphamide, doxorubicin, vincristine, and prednisone.

## RESULTS

### *Patient characteristics*

Patient characteristics are listed in Table 2. Twenty-two patients with locoregional relapse were restaged as IE–IIE. Twenty-two patients with distance relapse alone or both locoregional and distance relapse were staged as IIIE and IVE. The relapse time ranged from 3 to 84 months, with a median of 22 months. The ECOG scores of 11 patients (25%) were >1. There were not significant differences in clinical characteristics between patients with and without salvage treatment (Table 2).

### *Survival and prognostic factors*

After a median follow-up of 24 months (range, 6–108 months) in surviving patients, the estimated 1-, 3-, and