RESEARCH ARTICLE

Meta Analysis of Treatment for Stage IE~IIE Extranodal Natural Killer /T Cell Lymphomas in China

Hui Li*, Chun-Sen Wang, Xiao-Dong Wang

Abstract

Objective: To evaluate early treatment for extranodal natural killer/T cell lymphoma (ENK/TCL) in China and provide reference for clinical treatment of these patients. Methods: Computer-based retrieval was performed in PubMed, CNKI, CBM, VIP and WanFang Data to search for randomized controlled trials (RCTs) of treatment for early ENK/TCL, and a meta-analysis was conducted with RevMan 5.0 software. Results: A total of 11 RCTs, including 871 patients, were selected, of which the first radiotherapy had a higher complete response (CR) than the first chemotherapy [OR=14.16, 95%CI (8.68, 23.10), *P*<0.00001] and CR was not different between combined treatment group and radiotherapy group [OR=1.86, 95%CI (0.47, 3.58), *P*=0.61], but long-term survival rate was higher with combined treatment[OR=1.88, 95%CI (1.09, 3.19), *P*=0.02]. No difference in survival rate was observed between radio-chemotherapy and chemo-radiotherapy groups [OR=1.11, 95%CI (0.73, 1.69), *P*=0.63]. Conclusions: Radiotherapy is of great significance in the treatment of early ENK/TCL, but combined therapy could further enhance long-term survival rate of patients. This conclusion still requires further confirmation using RCTs with high quality and large sample size.

Keywords: Extranodal natural killer/T cell lymphoma - radiotherapy - chemotherapy - RCT - meta analysis

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Introduction

Extranodal natural killer (NK)/T cell lymphoma (nasal type ENK/TCL), including nasal and non-nasal NK/T cell lymphomas, accounts for 5%~15% of non-Hodgkin lymphoma (NHL). The disease onset is mainly between 40 and 50 years old with a male-female ratio of 2 ~ 3:1 and international prognostic indexes (IPI) score of 1 in early stage (IE~IIE) according to Ann Arbor staging. The incidence of ENK/TCL is relatively high in Asia with unique clinical features: it mainly occurs in the nasal cavity and sinuses and often invades into the upper respiratory tract and digestive tract, characterized by local necrotic changes in the area close to the facial midline, such as nose, pharynx and mouth; the patients develop the following symptoms and physical signs, including blood in nasal mucus, nasal obstruction, facial swelling, progressive inflammatory ulcer, necrosis, bone destruction, bone exposure, local severe radioactive pain and fever, etc. The clinical progress of this disease is fast with poor prognosis (Steven et al., 2008; Kohrt et al., 2009; Watanabe et al., 2010; Gualco et al., 2011)

At present, many studies have reported that ENK/TCL is sensitive to radiotherapy instead of chemotherapy containing Adriamycin; radiotherapy is the key to the successful treatment of local lesions (Kim et al., 2006); no significant difference in long-term survival rate of patients was observed between radiotherapy alone and radiotherapy combined with CHOP chemotherapy (Wang et al., 2007). Others have argued that both recent response rate and long-term survival rate of combined therapy are superior to those of radiotherapy (Lee et al., 2008; Zhang et al., 2013). To further clarify the proper treatment for these patients so as to achieve long-term remission rate and survival rate, we employed Cochrane systematic reviews to assess related randomized controlled trial (RCT) in China and provide reference for clinical application.

Materials and Methods

Inclusion and exclusion criteria

Design type: Design type was included in domestic RCT and quasi-RTC regardless of application of blind method and loss of follow-up. Language was Chinese.

Subjects: Subjects were patients diagnosed with stage IE~IIE ENK/TCL.

Intervention measures: Different treatments were compared: radiotherapy group, chemotherapy group, combined therapy group (including radio-chemotherapy group and chemo-radiotherapy group), radio-chemotherapy group (radiotherapy followed by chemotherapy) and chemo-radiotherapy group (chemotherapy followed by radiotherapy); the clinical trials constituted by multiple sets of intervention measures only provided the data of

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Table 1. General Data of Included Studies

First author	year	Gender (Male/Female, case)	Median age (Min~Max) (Years)	Stage	Interventions				Follow-up
					Radio-therapy	Chemo-therapy	Radio-chemotherapy	Chemo-radiotherapy	
Zheng Nai-ying	2012	30/28	46 (21~73)	23/35	20 cases	NA	38 Cases		Over five years
Nei Da-hong	2010	63/22	42 (4~76)	37/13	NA	20 cases	17 cases	48 cases	Over four years
LinYou-en	2009	37/15	47.5 (17-72)	37/15	26 cases	NA	NA	26 cases	3~6 cycles
Yao Bo	2006	77/39	39 (7~83)	95/21	22 cases	6 cases	41 case	47cases	Median time four years
Ma Hui-hui	2007	36/28	44 (15-80)	51/13	23 cases	NA	41 Cases		Median time 40 months
Wu Fueraikemu	2008	39/18	42 (15~74)	IE, 57 cases	15 cases	NA	20 cases	22 cases	Minimum five years
Zhao Yan-li	2011	33/13	41 (30-49)	42/4	5 cases	2 cases	39 Cases		Minimum five years
Wang Hu	2005	52/8	44 (12~74)	IE, 60 cases	9 cases	11 cases	9 cases	31 cases	Minimum five years
Jin Jing	2006	69/36	42 (9~72)	83/22	31 cases	3 cases	34 cases	37 cases	Median time 52 months
Yang Yong	2009	127/50	NA	138/39	6 cases	37 cases	6 cases	128 cases	Median time 47.5 months
Kang Gong-li	2012	61/25	48 (31~72)	72/14	13 cases	17 cases	21 cases	35 cases	Minimum five years

related intervention measures.

Outcome indicators: Judgment was in accordance with Response Evaluation Criteria in Solid Tumors or WHO criteria (Kinney Mc et al., 1999; Kamiyama T et al., 2009). Outcome indicators included complete response rate (CRR) and 1, 3, 5-year survival rate. CR was defined as the tumor completely disappeared after treatment; no tumor was observed in physical examination and imaging examination for more than one month. Survival rate was calculated from the first day of treatment to the date of death caused by any reason or the last day of follow-up.

Exclusion criteria: Descriptive research, research without control group and research with duplicate publication was excluded.

Retrieval strategy

Computer-based retrieval was performed in PubMed, CNKI (1989.1-2013.2), CBM (1989.1-2012.2), VIP (1989.1-2013.2) and WanFang Data (1989.1-2013.2); all references incorporated into literature were manually retrieved. Extranodal natural killer/T cell lymphoma and radiotherapy, chemotherapy were used as search terms.

Data extraction

Two evaluators independently screened the literature according to inclusion and exclusion criteria, extracted data and crosschecked. The disagreement in case was solved through discussion or ruled by a third party. Extracted data covered first author, published year, specific symptoms, intervention measures, course of treatment and clinical efficacy, etc.

Quality evaluation of included studies

Criteria for assessing risk of bias in Cochrane Handbook for Systematic Reviews (Version 5.1.0) was employed to evaluate methodological quality of included studies.

Statistical study

Statistical analysis of data was performed with RevMan 5.0 software provided by Cochrane collaboration. Effect size of efficacy utilized interval estimation and hypothesis test. Enumeration data was presented in odds ratio (OR) and its 95%CI was reported. Hypothesis test employed Z test and was described with Z values and *P* values; P≤0.05 between two groups was considered significant; the results of interval estimation and hypothesis test were shown in the forest plot. Heterogeneity test of included study was firstly carried out and $P<0.10$ (due to low power of homogeneity test, significant level was always defined as $\alpha=0.10$) was considered statistically significant. At the same time I^2 was used for quantitative analysis of heterogeneity: $I^2<25\%$ was low heterogeneity, $25\%\leq I^2\leq 50\%$ was moderate heterogeneity, $I^2>50\%$ was high heterogeneity. If the research had no statistical heterogeneity ($P\geq 0.10$, $I^2\leq 50\%$), the fixed effect model was selected for Meta analysis; if the research had statistical heterogeneity ($P<0.10$, $I^2>50\%$), random effect model could be used for Meta analysis.

Results

Retrieved result and characteristics of included studies

According to the retrieval strategy, a total of 442 related references were checked, among which 53 were preliminary screened after reading the title, abstract and excluding repetitive non-clinical studies and literature that was not related to treatments. Eventually 11 RCT were selected after going through the full articles, which included 871 patients with stage IE~IIE ENK/TCL who were divided into radiotherapy group, chemotherapy group, radio-chemotherapy group and chemo-radiotherapy group . The characteristics of included studies were shown in Table 1. There were no differences in gender, age, clinical stage between test and control groups (Table 1).

Quality evaluation of included studies

All included studies reported general conditions of patients with complete result data, but did not described random, blind method and loss of follow-up in details, as well as allocation concealment. Therefore, the overall evaluation was relatively low.

Efficacy and safety evaluation

Efficacy evaluation: Efficacy evaluation of 11 RCT was carried out from the following four aspects: first radiotherapy VS first chemotherapy; combined therapy VS radiotherapy; combined therapy VS chemotherapy; radio-chemotherapy VS chemo-radiotherapy. Evaluation index was CRR.

Among 11 RCT, four of them (Jin Jing et al., 2006; Yao Bo et al., 2006; Wu Fueraikemu et al., 2008; Nie Dahong et al., 2010; Kang Gongli et al., 2012) compared the efficacy between first radiotherapy and first chemotherapy

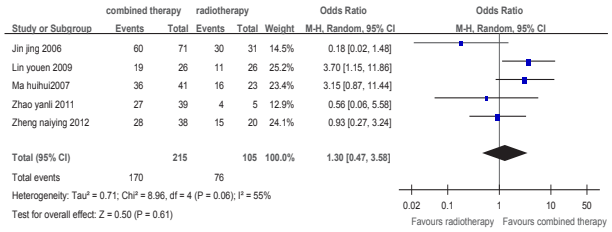

Figure 1. Meta Analysis of CRR Between First Radiotherapy and First Chemotherapy

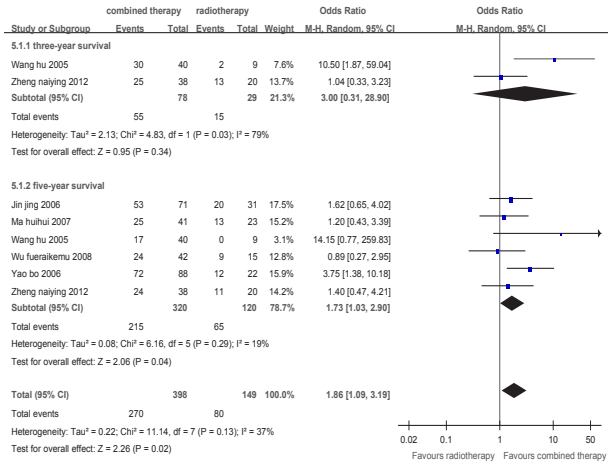

Figure 2. Meta Analysis of CRR Between Combined Therapy and Radiotherapy

in 431 patients, including 214 cases of radiotherapy and 217 cases of chemotherapy, and the results showed that 170 and 50 patients had complete response with CRR of 79.44% and 23.04% in first radiotherapy group and first chemotherapy group, respectively. No statistical heterogeneity was found among studies (P=88, I^2=0%), thus fixed effect model was used for Meta analysis. Combined analysis results suggested that CRR was significantly different [OR=14.16, 95%CI (8.68, 23.10), P<0.00001], i.e. first radiotherapy had higher CRR than first chemotherapy, shown in Figure 1.

Among 11 RCT, four of them (Jin et al., 2006; Ma et al., 2007; Lin et al., 2009; Zhao et al., 2011; Zheng et al., 2012) compared the efficacy between combined therapy and radiotherapy in 320 patients, including 215 cases of combined therapy and 217 cases of radiotherapy, and the results showed that 170 and 76 patients had complete response with CRR of 79.07% and 72.38% in combined therapy and radiotherapy groups, respectively. Statistical heterogeneity was found among studies (P=0.06, I^2=55%), thus random effect model was used for Meta analysis. Combined analysis results suggested that CRR had no statistical difference [OR=1.30, 95%CI (0.47, 3.58), P=0.61], i.e. combined therapy and radiotherapy groups had similar CRR, shown in Figure 2.

Among 11 RCT, three of them (Jin et al., 2006; Yang et al., 2009; Zhao et al., 2011) compared the efficacy between combined therapy and chemotherapy in 280 patients, including 238 cases of combined therapy and 42 cases of chemotherapy, and the results showed that 189 and 12 patients had complete response with CRR of 79.41% and 28.57% in combined therapy and chemotherapy groups, respectively. No statistical heterogeneity was found among

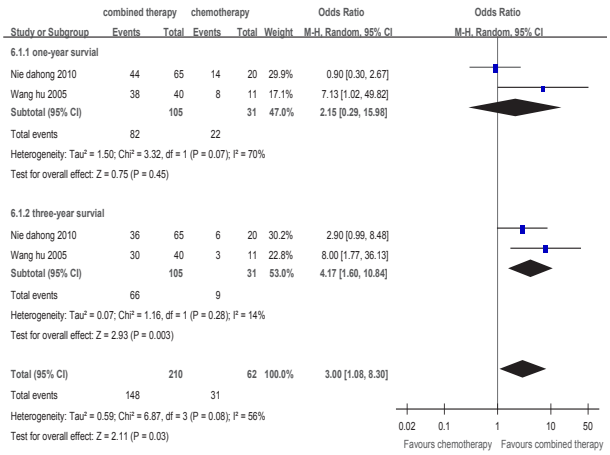

Figure 3. Meta Analysis of Survival Rate Between Combined Therapy and Radiotherapy

studies (P=0.99, I^2=0%), thus fixed effect model was used for Meta analysis. Combined analysis results suggested that CRR was significantly different [OR=9.52, 95%CI (4.44, 20.40), P<0.00001], i.e. combined therapy group had higher CRR than chemotherapy group.

Among 11 RCT, two of them (Yao Bo et al., 2006; Jin Jing et al., 2006) compared the efficacy between radio-chemotherapy and chemo-radiotherapy in 159 patients, including 75 cases of radio-chemotherapy and 84 cases of chemo-radiotherapy, and the results showed that 65 and 64 patients had complete response with CRR of 86.67% and 76.19% in radio-chemotherapy and chemo-radiotherapy groups, respectively. No statistical heterogeneity was found among studies (P=0.78, I^2=0%), thus fixed effect model was used for Meta analysis. Combined analysis results suggested that CRR had no statistical difference [OR=2.03, 95%CI (0.88, 4.68), P=0.10], i.e. radio-chemotherapy and chemo-radiotherapy groups had similar CRR.

Safety evaluation: Among 11 RCT, two of them (Yang Yong et al., 2009; Nie Dahong et al., 2010) reported untoward effects, which were mainly manifested as gastrointestinal symptoms, such as nausea and vomiting, myelosuppression, cutaneous reaction, oral mucosa reaction and throat reaction, or even massive hemorrhage of gastrointestinal tract and severe bone marrow suppression, etc. Chemo-radiotherapy group had highest incidence of side effects (21%), while radio-chemotherapy group had highest mortality (50%) (Lee et al., 2013), but Meta analysis was not conducted due to small number of reported cases.

Survival rate evaluation

One, three, five-year survival rates of included studies were assessed from the following three aspects: combined therapy VS radiotherapy; combined therapy VS chemotherapy; radio-chemotherapy VS chemo-radiotherapy.

Comparison of survival rate between combined therapy and radiotherapy groups: Among 11 RCT, two of them (Wang Hu et al., 2005; Zheng Naiying et al., 2012) compared three-year survival rate and six of them (Wang

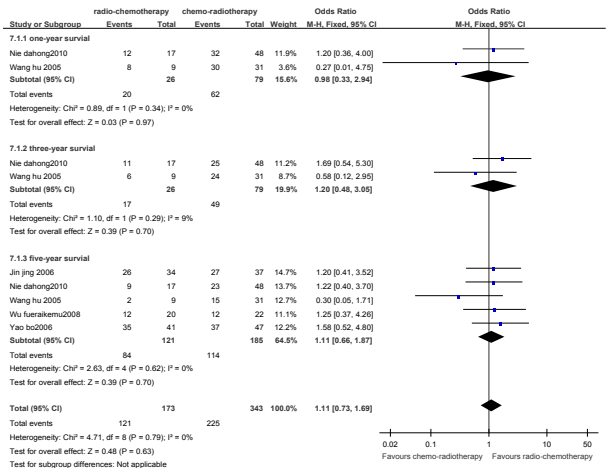

Figure 4. Meta Analysis of Survival Rate Between Combined Therapy and Chemotherapy

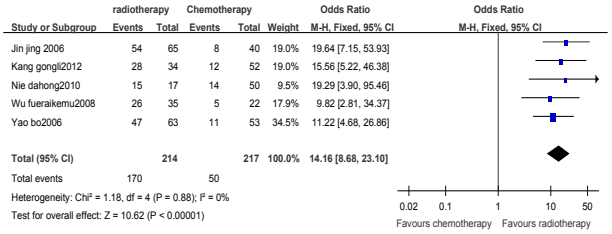

Figure 5. Meta Analysis of Survival Rate Between Radio-chemotherapy and Chemo-radiotherapy

Hu et al., 2005; Jin Jing et al., 2006; Yao Bo et al., 2006; Ma Huihui et al., 2007; Wu Fueraikemu et al., 2008; Zheng Naiying et al., 2012) compared five-year survival rate between combined therapy and radiotherapy groups in 547 patients, including 398 cases of combined therapy and 149 cases of radiotherapy, and the results showed that no statistical difference in three-year survival rate [OR=3.00, 95%CI (0.31, 28.90), *P*=0.34] but marked difference in five-year survival rate [OR=1.73, 95%CI (1.03, 2.90), *P*=0.04] were observed. Combined analysis results suggested that survival rates had statistical difference [OR=1.86, 95%CI (1.09, 3.19), *P*=0.002], i.e. combined therapy group had higher survival rate than radiotherapy group, shown in Figure 3.

Comparison of survival rate between combined therapy and chemotherapy groups: Among 11 RCT, two of them (Wang et al., 2005; Nie et al., 2010) compared one, three-year survival rates in 272 patients, including 210 cases of combined therapy and 62 cases of chemotherapy, and the results showed that no statistical difference in one-year survival rate [OR=2.15, 95%CI (0.29, 15.98), *P*=0.45] but marked difference in three-year survival rate [OR=4.17, 95%CI (1.60, 10.84), *P*=0.003] were observed. Combined analysis results suggested that survival rates had statistical difference [OR=3.00, 95%CI (1.08, 8.30), *P*=0.03], i.e. combined therapy group had higher survival rate than chemotherapy group, shown in Figure 4.

Comparison of survival rate between radio-chemotherapy and chemo-radiotherapy: Among 11 RCT, two of them (Wang Hu et al., 2005; Nie Dahong et al., 2010) compared one, three-year survival rates and five of them (Wang Hu et al., 2005; Yao Bo et al., 2006; Ma Huihui et al., 2007; Wu Fueraikemu et al., 2008; Nie Dahong et al., 2010) reported five-year survival rate in 516 patients, including 173 cases of radio-chemotherapy and 343 cases of chemo-radiotherapy, and the results showed that no statistical differences in one, three, five-year survival rates [OR=0.98, 95%CI (0.33, 2.94), *P*=0.97], [OR=1.20, 95%CI (0.48, 3.05), *P*=0.29], [OR=1.11, 95%CI (0.66, 1.87), *P*=0.70] were observed. Combined analysis results suggested that survival rate had no statistical difference [OR=1.11, 95%CI (0.73, 1.69), *P*=0.63], i.e. radio-chemotherapy and chemo-radiotherapy groups had similar survival rate, shown in Figure 5.

Discussion

ENK/TCL often occurs in East Asia and Latin America, but is relatively rare in Europe and the United States. Its morbidity is consistent with the rate of EB virus infection in the geographic distribution. Research in recent years has demonstrated that CD3 and CD56 present in the cytoplasm of theses tumor cells, which simulteneously express cytotoxic granule proteins, such as TIA-1 and EB virus antigen (Steven H et al., 2008; Au WY et al., 2009; Gill H et al., 2010; Gualco G et al., 2011; Shaoying Li et al., 2013) . ENK/TCL has poor prognosis and is influenced by many factors, including age, LDH value, the titer of Epstein-Barr virus (EBV) DNA, absolute lymphocyte count and the positive expression of CD30 (Au et al., 2004; Lee et al., 2005; Huang et al., 2011; Hong et al., 2012; Li et al., 2013) etc. The new study also shows that fasting blood glucose level in patients also affects their long-term survival (Cai et al., 2013).

So far, people at home and abroad have an agreement on the treatment for early ENK/TCL: radiotherapy alone is superior to chemotherapy alone (Kohrt et al., 2009; Kim et al., 2010), but radiotherapy alone likely causes disease recurrence even it easily relieves the patients (Li et al., 2011). It is pity that there is no systemic Meta analysis either in China or other foreign countries regarding whether combination of chemotherapy and radiotherapy can improve CRR and long-term survival of these patients and increase the incidence of untoward effects. We compared the efficacy, safety and survival rate of patients with early ENK/TCL who underwent radiotherapy, chemotherapy and combine therapy, and the results displayed that first radiotherapy had higher CRR than first chemotherapy (*P*<0.00001), but no statistical difference in CRR was observed between combined therapy and radiotherapy alone (*P*=0.61); while combined therapy group had higher long-term survival rate than radiotherapy group (*P*=0.002). These results indicated that as for short-term efficacy, chemotherapy had significance for patients with early ENK/TCL to achieve complete response; combined therapy extended long-term survival of patients although it could facilitate more patients to achieve complete response than radiotherapy did. In addition, the order of chemotherapy and radiotherapy in combined therapy had no effects on CRR and long-term survival rate of patients. At the same time, the side effects in combined therapy group were more than those of other groups,

which were manifested as gastrointestinal symptoms and myelosuppression. Therefore, comprehensive and detailed evaluation of patients should be done before the therapy, so as to apply individualized treatment and benefit the patients. With respect to the scheme of combine therapy, large number of studies (Lin et al., 2009; Gill et al., 2010; Zheng et al., 2012; Kang et al., 2012; ect) has reported that the radioactivity of 50Gy and1.8-2Gy/time are optimal for the patients, who poorly response to CHOP chemotherapy because these patients are not sensitive to anthracycline-based chemotherapy scheme duo to multidrug resistance induced by high expression level of *P*-glycoprotein (Wang et al., 2008). Whether etoposide or L-asparaginase-based chemotherapy that can overcome multidrug resistance mediated by *P*-glycoprotein should be applied still requires further research (Yong et al., 2009; Huang et al., 2011).

Included studies in our research have disadvantages as follows: (1) the overall methodological quality of 11 RCT was relatively low with high possibility of selection bias, performance bias and measurement bias; (2) there were some differences in the course of therapy and specific therapeutic measures, thus the studies had certain clinical heterogeneity, which might affect comprehensive analysis results.

In conclusion, the treatment of patients with early ENK/TCL in China was mainly radiotherapy. The combination of radiotherapy and chemotherapy had its advantages in further enhancing the long-term survival rate of patients, but considering that combined therapy likely brought more side effects, individualized treatment should be applied. At present, the conclusive Meta analysis has provided references for the clinical treatment of this disease, but further randomized, double-blind controlled trials with rigorous design, reliable methods and high quality are required in order to comprehensively, objectively and correctly evaluate the efficacy, safety and long-term survival rate of the treatment for early ENK/TCL.

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