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Research paper

Role of radiotherapy in patients with limited diffuse large B-cell lymphoma of Waldeyer's ring in remission after R-CHOP immunochemotherapy

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ABSTRACT

The standard treatment of waldeyer's ring DLBCL remains controversial. This retrospective study was designed to evaluate the role of consolidation radiotherapy (RT) in patients with stage I/II diffuse large B-cell lymphoma (DLBCL) limited in Waldeyer's ring (WR). We included 72 patients, 42 were treated with immunochemotherapy alone (CT group) and 30 were treated with immunochemotherapy followed by radiotherapy (CT + RT group). All patients received at least 3 cycles of R-CHOP regimen and achieved complete remission (CR) after immunochemotherapy. After 53 months median follow-up time, the 5-year progression-free survival (PFS) rates in CT + RT group vs. CT group were 93.3% vs. 92.5% (P = 0.896), the 5-year overall survival (OS) rates were 96.7% vs. 94.4% (P = 0.649). Patients with oropharyngeal primary had relatively better 5-year PFS and OS rates compared to nasopharyngeal primary (PFS: 98.2% vs. 73.3%, p = 0.001; OS: 100% vs. 79.0%, p < 0.001). Moreover, the primary site was the only independent prognostic factor for PFS in the multivariate analysis (p = 0.012, HR 16.858 [95% CI: 1.883–150.933]).

1. Introduction

Waldeyer's Ring (WR) is a circular band of lymphoid tissue and mainly consists of nasopharynx, oropharynx, tonsils and tongue base. It is the most common site of non-Hodgkin's lymphoma (NHL) in the head and neck and accounts for more than 50% of the lesion [1]. The most common histologic subtype of NHL in WR is diffuse large B cell lymphoma (DLBCL) [2]. Previous reports found that 92% of WR-DLBCL are limited (stage, I/II), and nearly 60% of patients present with tonsil as a primary site [2]. Radiation therapy is commonly used for the treatment of the limited type. However, researchers have found that although WR-DLBCL tend to be limited, it may still relapse at sites out of the radiation field [3,4]. Therefore, systemic chemotherapy combined with radiotherapy (RT) are more effective based on existing literatures [4–6].

Unfortunately, due to the special anatomical site of the WR, RT may cause acute or chronic toxicities, such as acute oral mucositis, dental decay, xerostomia and so forth. Oliver et al. reported that patients with limited WR-DLBCL lymphoma had prolonged xerostomia after treatment of RT [7]. Li et al. reported 57.4% of patients experienced late xerostomia after treatment of RT [8]. Mian et al. retrospectively analysed 184 WR-DLBCL patients in stage I and II who achieved CR/CRu (complete remission, CR / unconfirmed complete remission, CRu) after upfront anthracycline-containing chemotherapy. The results suggested RT did not prolong lymphoma-specific survival and disease-free

Abbreviations: WR, Waldeyer's ring; NHL, non-Hodgkin's lymphoma; DLBCL, diffuse large B-cell lymphoma; RT, radiotherapy; IFRT, Involved field radiation therapy; CT, immunochemotherapy; PET-CT, positron emission tomography-computed tomography; DFS, disease free survival; PFS, progression free survival; OS, overall survival; CR, complete remission; CRu, unconfirmed complete remission; WHO, World Health Organization; ECOG, Eastern Cooperative Oncology Group; PS, performance status; LDH, lactate dehydrogenase; IPI, International Prognostic Index; HR, hazard ratio; CI, confidence interval; Non-GCB, non-germinal center B-cell-like

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survival (DFS) and the authors concluded that consolidation radiotherapy are not necessary for those patients [9]. With the additional use of rituximab, the efficacy of systemic treatment in DLBCL is substantially improved in the past decades. Therefore, the necessity of applying RT after immunochemotherapy in treating limited WR-DLBCL remains controversial and requires further investigation.

2. Materials and methods

2.1. Patients

From September 2008 to May 2016, 146 patients in our center with limited WR-DLBCL achieving CR after treatment of rituximab and anthracycline-containing immunochemotherapy were identified. Seventy-four patients were excluded because of inadequate medical records, with mediastinal and/or axillary lymph nodes involvements, receiving radiotherapy before chemotherapy or with follow-up time of fewer than 24 months. Finally, 72 patients (from September 2008 to May 2014) were included and analysed, 32 patients (44.44%) were initially staged with PET/CT while others were staged with CT and MRI. DLBCL that mainly affected WR with (stage II) or without (stage I) involvement of neck lymph nodes (cervical and supraclavicular) and adjacent extranodal structures are defined as limited WR-DLBCL and staged with the Ann Arbor system [10]. Histologic diagnosis was performed according to the World Health Organization (WHO) classification of 2008 [11]. The response was assessed according to the Cheson response criteria for malignant lymphoma in 2008 [12]. All patients achieved CR after immunochemotherapy and among them 30 patients received subsequent RT and 42 patients did not.

2.2. Treatment

All patients were treated with 3–8 cycles of anthracycline-based immunochemotherapy regimen (median: 6 cycles) with (CT + RT group) or without (CT group) RT afterwards. The median dose of RT was 3600cGy (range, 1620-4000cGy).

2.3. Statistical analysis

Baseline characteristics were compared using Chi-square tests for categorical variables between CT + RT and CT groups. The duration of PFS and OS was defined according to Cheson et al. [13]. The Kaplan-Meier method was used to plot PFS and OS curves. The log-rank test was used to investigate the impact of different treatments on patients' survival. Univariate analysis was performed to determine the influence of clinical factors on patients' PFS and OS. Variables with P value less than 0.20 in univariate analysis and those used to be reported significant were then analysed by multivariate analysis using Cox proportional hazards model.

Each factor with a P value less than 0.05 was considered statistically significant. All statistical analyses were performed with Statistical Package for the Social Sciences (SPSS) software v.19.0.

3. Results

3.1. Study participants

Demographic data are summarized in Table 1. A total of 72 patients were included in this retrospective study. Median age was 57 years in both groups. There were 24 patients with stage I and 48 patients with stage II. Among 6 patients who were diagnosed with B symptoms, 3 were in CT + RT group and 3 were in CT group. All patients were in good performance status [Eastern Cooperative Oncology Group (ECOG) score 0–1 and International Prognostic Index (IPI) 0–2]. The most commonly involved site is the tonsil (62.5%). Among patients with tonsil involvement, three had adjacent structure involvements, two of which were in the CT + RT group and one in the CT group. No bulky disease (> 7.5 cm) was observed in either group. No statistical difference in baseline characteristics was observed between the two groups.

Table 1
Demographic data (N = 72).

	CT + RT		CT		P value
	No.	%	No.	%	
No. of patients	30		42		
Age, years					
Median (range)	57 (29–79)		57 (22–72)		
≤ 60	21	70.0	32	76.2	0.557
> 60	9	30.0	10	23.8	
Gender					
Male	18	60.0	22	52.4	0.521
Female	12	40.0	20	47.6	
Primary site					
Oropharynx	21	70.0	36	85.7	0.106
Nasopharynx	9	30.0	6	14.3	
B symptoms					
Yes	3	10.0	3	7.1	1.000
No	27	90.0	39	92.9	
Ann Arbor Stage					
I	9	30.0	15	35.7	0.612
II	21	70.0	27	64.3	
ECOG PS					
0	17	56.7	24	57.1	0.968
1	13	43.3	18	42.9	
LDH level					
Normal	29	96.7	40	95.2	1.000
Elevated	1	3.3	2	4.8	
IPI					
0	21	70.0	31	73.8	0.767
1	9	30.0	10	23.8	
2	0	0.00	1	2.4	

CT: immunochemotherapy, RT: radiotherapy, PS: performance status, LDH: lactate dehydrogenase, IPI: International Prognostic Index.

3.2. Treatment information

All patients were treated with a median of six cycles of anthracycline-based immunochemotherapy regimen (range, 3–8 cycles). 96.7% of patients in CT + RT group and 100% in CT group had no less than 4 cycles of chemotherapy (CHOP), and most patients (90% in CT + RT group and 100% in CT group) received 4 or more cycles of rituximab. 66.7% of patients in CT + RT group received 6–8 cycles of immunochemotherapy. The immunochemotherapy regimens and number of cycles received by CT + RT and CT groups were listed in Table 2.

Forty-two patients were treated with immunochemotherapy alone (CT group), while 30 patients were treated with combined modality (CT + RT group). Involved field radiation therapy (IFRT) were used in CT + RT group, including WR, lymphatic drainage area and adjacent

Table 2
The immunochemotherapy regimens and number of cycles received by CT + RT and CT groups.

Immunochemotherapy	Cycles	CT + RT Group N = 30		CT Group N = 42	
		No.	%	No.	%
RCHOP	3	3	10	0	0
	4	7	23.3	5	11.9
	6	19	63.3	35	83.3
	8	1	3.3	2	4.8

CT: immunochemotherapy, RT: radiotherapy.