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Original Article

Standard R-CHOP Therapy in Follicular Lymphoma and Diffuse Large B-Cell Lymphoma

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The introduction of rituximab (R) has measurably improved the outcome of patients with follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL). To evaluate the outcome of patients with FL and DLBCL under R plus CHOP therapy, we performed a retrospective analysis in Yokohama City University Hematology Group in Japan. Five hundred and twenty-six patients (158, FL ; 368, DLBCL) were scheduled to undergo primary therapy with 6 cycles of full-dose R-CHOP therapy with curative intent. The median observation periods in living patients with FL and DLBCL were 45 months and 43 months, respectively. The complete response, 5-year progression-free survival (PFS), and 5-year overall survival (OS) rates were 86%, 50%, and 92% in the FL group, and 89%, 72%, and 80% in the DLBCL group, respectively. Although PFS was significantly better in the DLBCL group than in the FL group, OS was significantly better in FL patients. We also found that the OS and PFS of grade 3 FL patients were not statistically different from those with grade 1-2. These findings indicate that all grades of FL should be categorized simply as "FL" with regard to R-CHOP therapy. Our results also demonstrate the incurability of FL (grade 1-3B), even with R-CHOP therapy. 〔*J Clin Exp Hematop 53(2) : 121-125, 2013*〕

Keywords: diffuse large B-cell lymphoma, follicular lymphoma, R-CHOP

INTRODUCTION

In almost all cases, follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL) are CD20-positive. Since the introduction of rituximab (R) treatment, which targets CD20, the outcome of patients with FL[1] or DLBCL[2,3] has improved noticeably. Indeed, treatment with R-CHOP chemoimmunotherapy [50 mg/m^2 doxorubicin (adriamycin) on day 1, 750 mg/m^2 cyclophosphamide on day 1, 1.4 mg/m^2 (maximum 2.0 mg/body) vincristine on day 1, 100 mg/body of prednisolone on days 1-5, and 375 mg/m^2 R per cycle] is currently one of the most frequently used regimens for DLBCL treatment and is one of the most common combination regimens used to treat FL.[1,4] We therefore undertook a retrospective analysis of the outcomes of patients with FL or DLBCL who were uniformly treated using the standard R-CHOP regimen to evaluate its benefit. The prognosis of grade 3 FL was also evaluated and discussed.

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MATERIALS AND METHODS

This study was approved by Yokohama City University Hospital Clinical Research Ethics Board. The procedures of this study were in accordance with the Helsinki Declaration. The Yokohama City University Hematology Group in Japan has uniformly and curatively treated patients with FL, except stage 1 FL, and DLBCL since 2001 and 2003, respectively, with 6 cycles of standard R-CHOP therapy for 21 days. We initiated R-CHOP therapy immediately after the diagnosis in patients with FL in stage 2-4 without a watchful waiting strategy. We collected the FL patients between 2001 and 2009, and DLBCL patients between 2003 and 2009. In these

periods, 752 patients were treated (198, FL ; 554, DLBCL), and 526 of these patients (158, FL ; 368, DLBCL) were enrolled in this study. The eligibility criteria for the analysis were patients with FL (stage 2-4) or DLBCL (any stages) who had initially been treated with full-dose R-CHOP therapy with curative intent. Patients who required more than 20% dose reduction were excluded. Actually, the most frequent cause of exclusion was dose reduction of the drugs. Those with special forms of DLBCL, such as intravascular lymphoma, primary mediastinal large B-cell lymphoma and T-cell-rich B-cell lymphoma, and those with human immunodeficiency virus infection were also excluded from this study. Although our study was not a prospective clinical study, we had registered newly diagnosed patients with lymphoma in our database 3 times a year, and the treatment protocol was fixed in advance. We therefore believe that our study resembles a prospective one to some degree. All included patients were scheduled to undergo primary therapy with 6 cycles of full-dose R-CHOP in 7 hospitals. Clinical staging was performed according to the Ann Arbor system, by using the data of physical examination ; computed tomography of the neck, chest, abdomen and pelvis ; bone marrow aspiration and biopsy. When required, the data of endoscopic examination of the upper and/or lower gastrointestinal tract, lumbar puncture, magnetic resonance imaging of the brain, gallium scintigram and positron emission tomography were used for staging. Patients who had partial remission (PR) after the 4 initial cycles were administered 8 R-CHOP cycles in total, while patients who did not achieve PR after the 4 initial R-CHOP cycles or those who exhibited disease progression at any given time received salvage therapy. In these cases, the time point dealt with was that at disease progression. Additional local irradiation was also performed in patients with PR or complete remission (CR) if deemed necessary by the attending physician. No patients received maintenance therapy with R. Patients with DLBCL who achieved CR but were initially at risk of central nervous system (CNS) involvement also received methotrexate (15 mg) and hydrocortisone (25 mg) 4 times intrathecally for CNS prophylaxis. Central pathological reviews were not performed, and only individual institutional diagnoses according to the World Health Organization classification were used in subsequent analyses.

Univariate associations between histology (FL or DLBCL) and individual clinical features were analyzed using Chi-square test. The Mann-Whitney U test was used between ordered groups. Survival curves were compared using the log-rank test. A *P*-value below 0.05 was considered to indicate a significant difference.

RESULTS

Patient characteristics are shown in Table 1. In the FL group, 60 patients were at low risk (L) ; 60, at low-intermediate risk (LI) ; 26, at high-intermediate risk (HI) ;

Table 1. Patient characteristics

Clinical data	Follicular lymphoma (FL)				DLBCL	FL vs DLBCL *p* value
	All grades	Grade 1-2	Grade 3a	Grade 3b		
Number	158	126	20	12	368	
Median age, years (range)	57 (25-76)	57 (25-76)	59 (34-72)	50 (32-70)	64 (18-80)	< 0.001
Male (%)	51	52	35	67	57	NS
IPI factors						
Age greater that 60 years, %	35	37	30	25	62	< 0.001
PS 2-4, %	3	4	5	0	15	< 0.001
Elevated LDH, %	30	26	50	42	49	< 0.001
Stage III/IV, %	80	82	70	75	43	< 0.001
More than 1 extranodal site, %	37	36	35	50	29	NS
IPI						
Low, %	38	38	35	42	43	
Low-intermediate, %	38	41	35	17	25	
High-Intermediate, %	16	14	20	33	16	0.005
High, %	8	7	10	8	16	
FLIPI*						
Low, %	29	28	21	45	NA	
Intermediate, %	32	35	32	10	NA	
High, %	39	37	47	45	NA	

DLBCL, diffuse large B-cell lymphoma ; IPI, international prognostic index ; PS, performance status ; LDH, lactate dehydrogenase ; FLIPI, follicular lymphoma international prognostic index.

*, FLIPI is not evaluable in 7 patients.

and 12, at high risk (H), as determined using the International Prognostic Index (IPI).[5] According to the FL-IPI,[6] 43 patients were classified as L ; 49, as intermediate risk ; and 59, as H. The risk of 7 patients was not determined. Ten patients in either PR or CR received additional local irradiation after R-CHOP therapy, while none received CNS prophylaxis. Twelve deaths were observed among the FL patients during the observation period (median, 45 months in alive patients), 10 of which were due to the lymphomas. In the DLBCL group, 158 patients were classified as L ; 93, as LI ; 57, as HI ; and 60, as H, according to the IPI,[5] while 47 patients were classified as very good ; 204, as good ; and 117, as poor according to the R-IPI.[7] Thirty-seven patients received additional local irradiation during PR and CR following the completion of R-CHOP therapy. CNS prophylaxis was performed in 42 patients who achieved CR and had an initial CNS risk. During the observation period (median, 43 months in alive patients), 58 DLBCL patients died, 50 of whom due to the lymphoma. In terms of the background, the patients older than 60 years ($P < 0.001$), with poor PS ($P < 0.001$) and with elevated LDH ($P < 0.001$) were more common in the DLBCL group. In contrast, the patients with advanced stage ($P < 0.001$) were more common in the FL group.

When the survival rates of the study participants were examined, it was found that the CR, 5-year progression-free survival (PFS) and 5-year overall survival (OS) rates of the FL and DLBCL groups were 86%, 50% and 92%, and 89%, 72% and 80%, respectively. Interestingly, although the PFS rate of the DLBCL patients was significantly higher than that of patients with FL (Fig. 1A, $P = 0.001$), patients in the FL group had a significantly greater OS (Fig. 1B, $P = 0.006$). Furthermore, when the PFS (Fig. 1C) and OS (Fig. 1D) of patients with different grades of FL were compared, no significant differences between grade 1-2 FL and grade 3 FL were observed. This was also found to be the case when the PFS (Fig. 1E) and OS (Fig. 1F) of grade 1-3a FL patients were compared to those of grade 3b FL patients.

DISCUSSION

The findings of our study are similar to those of previous reports that examined the use of R-CHOP therapy in the treatment of FL[1] and DLBCL[7], including one that specifically examined the treatment of grade 3 FL.[8] In our study, approximately 70% of the DLBCL patients who were treated with R-CHOP therapy were cured, while the FL patients were generally incurable, albeit with the limitations of this study of its retrospective nature and lack of a pathological review. Furthermore, although patients with grade 1-2 and grade 3 FL were found to have similar outcomes, this outcome was inferior to that obtained in DLBCL patients in terms of PFS. As for grade 3 FL, the PFS curve was apparently worse than that in DLBCL. Similar results were shown even in FL grade 3B patients, although it was difficult to evaluate the results because of the relatively small number of patients with FL grade 3B. These findings suggest the potential incurability of FL grade 3 patients by R-CHOP. This is a warning for clinicians who are likely to treat patients with grade 3 FL as well as patients with DLBCL who have around 70% curability by R-CHOP.

Various prognostic markers for DLBCL have been evaluated since the introduction of R. Bcl-2, a marker of the germinal center, has also been identified as a prognostic indicator of poor DLBCL outcome following CHOP therapy ; however, it is possible to overcome resistance in DLBCL through the addition of R.[9] Despite this, the addition of R to CHOP did not affect Bcl-6 protein expression,[10] suggesting that the addition of R to CHOP may only be beneficial in Bcl-6-negative DLBCL. This was also found in a study that focused on *BCL6* rearrangement.[11] Furthermore, although the evaluation of these factors was not available in our multicenter retrospective study, we recently evaluated the prognostic value of *BCL2* and *BCL6* rearrangement for the efficacy of R-CHOP therapy in patients with confirmed chromosomal abnormalities and found no correlation with the outcome.[12] On the other hand, rearrangement of *MYC* is reported to be a definite poor prognostic marker[13] and the evaluation of *MYC* is important in the R-era.

In conclusion, standard R-CHOP therapy is effective for patients with both FL and DLBCL, with the 5-year OS rate exceeding 80% for both groups. However, in the FL group, the PFS did not show a plateau, suggesting the incurability of this lymphoma with R-CHOP therapy. Despite this, the long OS observed suggests that salvage therapy is effective in the treatment of FL patients. This study also suggests that all grades of FL should be categorized the same in regards to R-CHOP therapy since the OS and PFS in patients with grade 3 FL were similar to those in patients with grade 1-2 FL.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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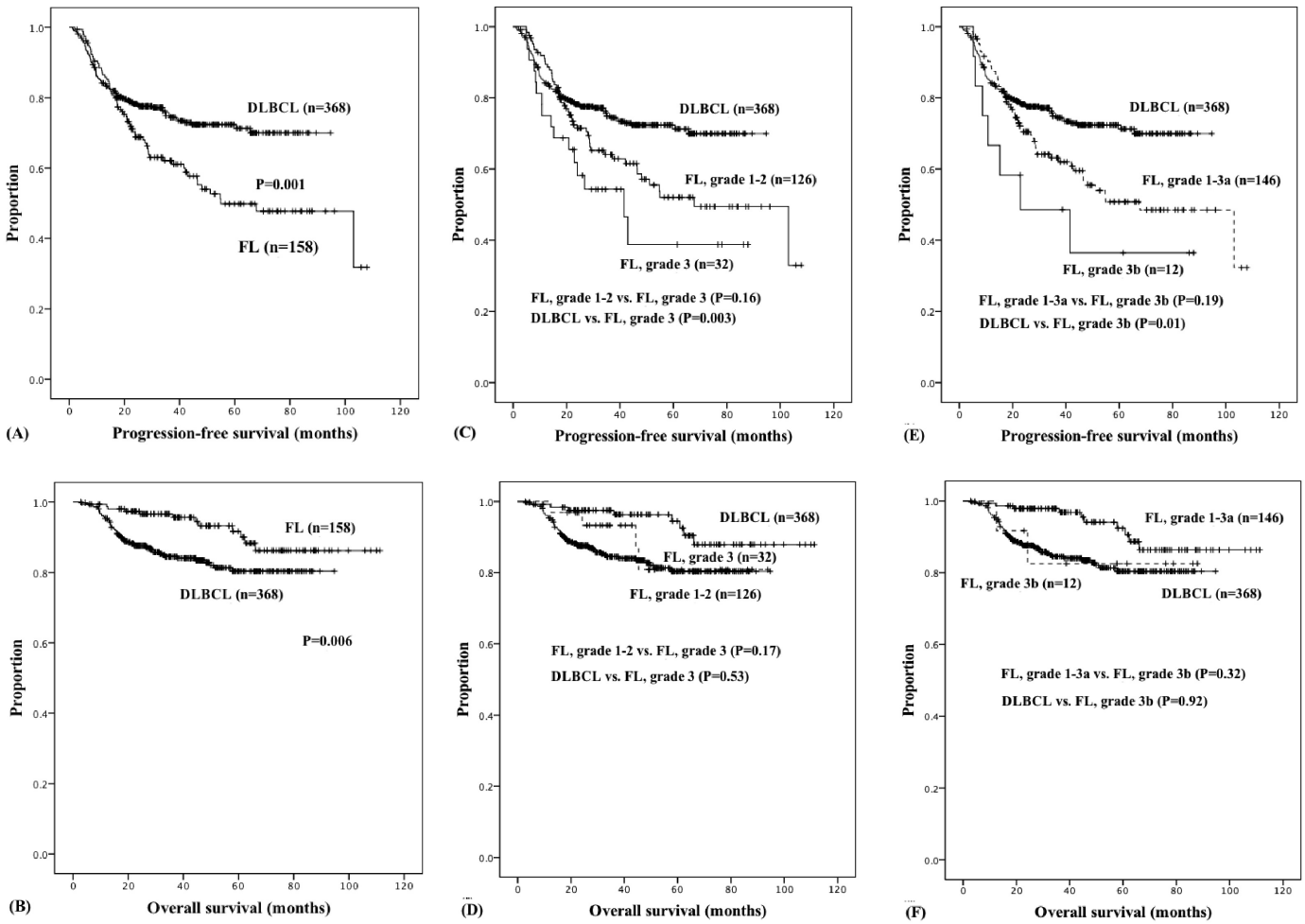

Fig. 1. The progression-free survival (PFS) and overall survival (OS) of follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL) patients following R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) therapy. The PFS (*1A*) and OS (*1B*) of FL and DLBCL patients after the initiation of R-CHOP therapy demonstrated that PFS is significantly better in DLBCL patients, while the 5-year OS of FL patients, with a rate of 93%, is significantly better than that of DLBCL patients. When only grade 3 FL patients are considered, the PFS (*1C*) of these patients is significantly worse than that of DLBCL, but the OS (*1D*) is not significantly different compared with that of grade 1-2 FL or DLBCL. This is also observed when the PFS (*1E*) and OS (*1F*) in grade 3b FL patients are compared with those of either grade 1-3a FL or DLBCL patients.

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