Post-treatment PET–CT Findings may Predict the Prognosis of DLBCL with a Bulky Mass

Hiroataka Takasaki · Wataru Yamamoto · Yoshimi Ishii · Hiroyuki Takahashi ·
Reina Watanabe · Taishi Harada · Rika Kawasaki · Chizuko Hashimoto ·
Shigeki Motomura · Naoto Tomita · Yoshiaki Ishigatsubo · Rika Sakai

Received: 24 January 2014 / Accepted: 20 November 2014 / Published online: 3 December 2014
© Indian Society of Haematology & Transfusion Medicine 2014

Abstract We retrospectively analyzed the prognosis of patients with diffuse large B cell lymphoma (DLBCL) and a bulky mass at diagnosis. We retrospectively analyzed clinical data for 29 consecutive DLBCL patients with an initial bulky mass receiving R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) therapy from 2004 to 2011. Bulky disease was defined as a measurable tumor mass >10 cm in diameter or a mediastinal mass >1/3 of the chest diameter. Patients with primary mediastinal large B-cell lymphoma were excluded. The median age was 65 years (20–78 years) and the maximum tumor diameter was 11.5 cm (10.0–17.0 cm). Complete response and partial response were achieved in 14 patients each, while 1 patient had progressive disease. The 3-year overall survival (OS) rate and progression-free survival (PFS) rate were 66 and 56 %, respectively. Findings on post-treatment positron emission tomography-computed tomography (PET–CT) were significantly associated with OS (34 % for patients with abnormal uptake vs. 75 % for those without, $P = 0.014$), and were also associated with PFS (36 vs. 83 %, respectively, $P < 0.001$). Nine patients with a single site of abnormal uptake on PET–CT underwent radiotherapy and 5 of them subsequently relapsed. An initial bulky mass does not indicate a

poor prognosis of DLBCL. However, the post-treatment PET–CT findings may have predictive value in DLBCL patients with a bulky mass.

Keywords Diffuse large B-cell lymphoma · Bulky mass · PET–CT

Introduction

In the pre-rituximab era, most (but not all) researchers reported that bulky disease had an influence on the outcome in patients with aggressive lymphoma and diffuse large B-cell lymphoma (DLBCL) [1–7]. Divergent results were obtained because of differences in the patient populations studied. After R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) became the standard treatment, the prognosis of DLBCL with a bulky mass was re-examined. The US Intergroup trial did not demonstrate that tumor size was an important indicator in DLBCL patients receiving R-CHOP therapy [8], and bulky disease (a mass ≥ 10 cm in diameter) was not identified as a prognostic factor in the Groupe d'Etude des Lymphomes de l'Adulte (GELA) Study [9]. However, a recent extrapolative analysis of the MabThera International Trial Group (MInT) study found a stronger influence of the maximum size of bulky masses on the outcome of patients in the rituximab era [10]. Thus, the influence of a bulky mass on the outcome of DLBCL patients receiving R-CHOP therapy is still unclear.

In patients with a bulky mass, residual tumor is often detected by CT at the end of treatment, and it is sometimes difficult to determine whether additional treatment such as radiotherapy should be performed or not. According to the NCCN guidelines (2013 ver. 1), if PET–CT is positive at

H. Takasaki (✉) · W. Yamamoto · Y. Ishii · H. Takahashi ·
R. Watanabe · T. Harada · R. Kawasaki · C. Hashimoto ·
S. Motomura · R. Sakai
Department of Medical Oncology, Kanagawa Cancer Center,
2-3-2 Nakao, Asahi-ku, Yokohama 241-8515, Japan
e-mail: takasakih@kcch.jp

N. Tomita · Y. Ishigatsubo
Department of Internal Medicine and Clinical Immunology,
Graduate School of Medicine, Yokohama City University,
Yokohama, Japan

the end of treatment for limited DLBCL with a bulky mass (>10 cm), radiotherapy should be considered (Category 1). In patients with advanced DLBCL and a bulky mass, however whether radiotherapy is required should be determined on a case-by-case basis (Category 2B).

In the present study, we retrospectively investigated the outcome of DLBCL patients with a bulky mass and also assessed the accuracy of predicting the prognosis based on the post-treatment PET–CT findings.

Materials and Methods

Bulky disease was defined as a measurable mass ≥ 10 cm diameter or a mediastinal mass $>1/3$ of the chest diameter [11]. If a bulky mediastinal mass showed invasion of the surrounding structures and was pathologically diagnosed as DLBCL, the patient was considered to have primary mediastinal large B-cell lymphoma and was excluded from this study. From February 2004 to July 2011, 201 consecutive patients who had untreated DLBCL received R-CHOP therapy (cyclophosphamide 750 mg/m^2 on Day 1; doxorubicin 50 mg/m^2 on Day 1; vincristine 1.4 mg/m^2 on Day 1 (max 2 mg); prednisolone 60 mg/m^2 on Days 1–5; and rituximab 375 mg/m^2 on Day 15) for up to 6–8 cycles without weight loss [12]. Treatment was given in 21 day cycles. Among these 201 patients, 29 had a bulky mass. We compared treatment outcomes between the bulky mass group ($n = 29$) and the non-bulky mass group ($n = 172$). Stage I, II of Ann arbor classification limited-stage, Stage III, IV was defined as advanced stage. We also studied prognostic factors and the accuracy of predicting the outcome based on detection of residual disease at the end of R-CHOP therapy in the bulky mass group. The criteria of Cheson et al. were used to assess the effectiveness of treatment [13]. Positron emission tomography-computed tomography (PET–CT) with ^{18}F -fluorodeoxyglucose performed before initiation of R-CHOP therapy and 6–8 weeks after the completion of R-CHOP therapy. A negative PET scan was defined as showing no abnormal uptake or minimal residual uptake. Mediastinal blood pool activity was used as the reference to define PET positivity. If a residual mass ≥ 2.0 cm in greatest transverse diameter (or a smaller residual mass or normal-sized lymph node) showed higher uptake than the blood pool, the PET scan was considered to be positive. All PET–CT scans were reviewed by a single nuclear medicine physician.

Overall survival (OS) was defined as the interval from diagnosis until death from any cause or the final date of observation. Progression-free survival (PFS) was defined as the interval from diagnosis until relapse or progression of lymphoma, death from any cause, or the final date of observation (if progression or death did not occur). Survival was

calculated by the Kaplan–Meier method, and differences in survival were assessed by the log-rank test. The relative risk and its 95 % confidence interval (CI) were determined, as well as P values. All P values were two-sided, with significance being accepted at $P \leq 0.05$. Statistical analyses were performed with R2.10.1 software (R Foundation for Statistical Computing, Vienna, Austria). This study was approved by the institutional review board of Kanagawa Cancer Center.

Results

Patient Profile

The median age of the patients with a bulky mass was 65 years (range 20–78 years). The most frequent site of a bulky mass at presentation was the mesenteric lymph nodes (55 %) and the maximum tumor diameter was 11.5 cm (10.0–17.0 cm). The characteristics of the 29 patients are presented in Table 1. The number of patients in stages I, II, III, and IV was 3, 10, 7, and 9, respectively. There were no significant differences of stage distribution between the two groups ($P = 0.625$). The International prognostic index (IPI) risk category was low, low-intermediate, high-intermediate, and high for 6, 10, 8, and 5 of the patients, respectively. Patients with a bulky were more likely to be in poor risk categories, though this was not statistically significant ($P = 0.069$). Patients with a bulky mass were significantly more likely to have a performance status (PS) ≥ 2 (45 vs. 19 %, $P = 0.005$), elevation of serum lactate dehydrogenase (LDH) (86 vs. 61 %, $P = 0.007$), and B symptoms (38 vs. 17 %, $P = 0.017$).

Outcome of Patients with and Without a Bulky Mass

The median follow-up time for surviving patients was 3.2 years (range: 0.7–8.0 years). Figure 1 shows the 3-year OS and PFS of patients who had limited disease with or without a bulky mass. There were no significant differences between the two groups (90 % [95 % CI 84–98] vs. 69 % [95 % CI 45–100] [$P = 0.105$] and 83 % [95 % CI 75–92] vs. 77 % [95 % CI 57–100] [$P = 0.499$], respectively). Figure 2 shows the 3-year OS and PFS of patients who had advanced disease with or without a bulky mass. Again, there were no significant differences between the two groups (76 % [95 % CI 67–87] vs. 66 % [95 % CI 43–100] [$P = 0.279$] and 72 % [95 % CI 63–83] vs. 28 % [95 % CI 65–100] [$P = 0.096$], respectively).

Prognosis of Patients with a Bulky Mass

When prognostic factors for OS and PFS were assessed by univariate analysis, the findings on post-treatment PET–CT

Table 1 Patient characteristics (*n* = 201)

Variables	DLBCL with a bulky mass (<i>n</i> = 29)		DLBCL without a bulky mass (<i>n</i> = 172)		P value
	No. of patients	(%)	No. of patients	(%)	
Median age (range)	65 (20–78)		64 (19–84)		0.765
Gender					
Male	15	52	93	54	0.974
Female	14	48	79	46	
Performance status					
0–1	16	55	139	81	0.005
≥ 2	13	45	33	19	
LDH					
Normal	4	14	67	39	0.007
Elevated	25	86	105	61	
Stage					
I	3	10	29	17	0.625
II	10	34	60	35	
III	7	25	43	25	
IV	9	31	40	23	
Extranodal lesion					
0–1	20	69	119	69	0.847
≥ 2	9	31	53	31	
Bone marrow involvement					
Yes	4	14	15	8	0.602
No	25	86	157	92	
B symptoms					
A	18	62	143	83	0.017
B	11	38	29	17	
International prognostic index					
Low risk	8	28	72	42	0.069
Low-intermediate risk	5	17	39	23	
High-intermediate risk	6	21	31	18	
High risk	10	34	30	17	

DLBCL diffuse large B-cell lymphoma, *LDH* lactate dehydrogenase

were statistically associated with OS (34 % [95 % CI 12–94] for PET-positive patients vs. 75 % [95 % CI 43–100] for PET-negative patients [*P* = 0.014]) and with PFS (36 % [95 % CI 18–72] vs. 83 % [95 % CI 58–100], respectively [*P* < 0.001]) (Fig. 3; Table 2). In contrast, the age, PS, LDH, stage, and extranodal disease were not significantly associated with either OS or PFS.

PET–CT was performed before treatment in 27 patients, but not in 2 patients with rapid disease progression. At the end of treatment, 28 patients underwent PET–CT, excluding 1 patient with disease progression, and 14 patients had no abnormal uptake of FDG. Although 5 (2 with limited disease and 3 with advanced disease) of the 14 patients still had residual tumors on CT, none of them received additional treatment (including radiation therapy) and all of them remained in remission at the end of the observation period. The other 14 patients had abnormal FDG uptake at

the completion of R-CHOP therapy. Nine of these patients (3 with limited disease and 6 with advanced disease) still had a bulky mass on CT, and 5 of them developed recurrence after receiving radiotherapy.

Discussion

The presence or absence of a bulky mass is not included in the IPI, which is widely used for predicting the prognosis of DLBCL. However, a poor prognosis has been reported for DLBCL patients with large extranodal lesions or those with tumors more than 5.0–10.0 cm in diameter [10, 14, 15]. One problem is the lack of a generally accepted definition of a bulky mass. In the present study, we defined a bulky mass as a tumor ≥ 10 cm diameter or a mediastinal mass $> 1/3$ of the chest diameter, according to the

Fig. 1 Overall survival of all patients. **a** Limited disease. **b** Extensive disease

Fig. 2 Progression-free survival of all patients. **a** Limited disease. **b** Extensive disease

Cotswolds classification, which is widely used for clinical staging of malignant lymphoma. As a result, we found that DLBCL patients with a bulky mass tended to have features that were suggestive of progressive disease, including a worse PS, B symptoms, a higher serum LDH level, and a higher IPI risk than in the patients without a bulky mass. However, the presence of a bulky mass was not correlated with a poor prognosis among patients with either limited disease or advanced disease.

Among DLBCL patients with a bulky mass before treatment, regardless of whether or not a residual mass was detected by CT after R-CHOP therapy, those who were negative for abnormal uptake on PET-CT had a good prognosis without additional treatment, whereas those with

abnormal uptake had a poor prognosis. According to Juweid et al., about half of the patients with DLBCL achieving PR on post-treatment CT showed no uptake of FDG, and their progression-free survival was almost equivalent to that of CR patients without additional treatment and was better than that of patients with FDG uptake [16]. There have been few reports about the outcome of DLBCL with a bulky mass based on post-treatment PET-CT findings. Our results suggested that performing PET-CT at the end of R-CHOP therapy may be useful for predicting the prognosis, similar to the case for DLBCL without a bulky mass. In contrast, stage, and IPI risk were not significantly associated with either OS or PFS. This analysis of small number of patient, it is considered one of the causes.

Fig. 3 Overall survival and progression-free survival of patients with a bulky mass stratified by post-treatment PET-CT findings. **a** Overall survival. **b** Progression-free survival

Table 2 Prognostic factors with a bulky mass (univariate analysis)

Variables	No. of patients	3-year OS		3-year PFS	
		%	P value	%	P value
Age, years					
< 60	13	66	0.504	58	0.876
≥ 60	16	60		47	
Performance status					
0–1	16	78	0.357	62	0.967
≥ 2	13	53		46	
Stage					
Limited stage	13	83	0.388	77	0.163
Extensive stage	16	66		28	
LDH					
Normal	4	100	0.096	100	0.101
Elevated	25	57		45	
International prognostic index					
Low, low-intermediate risk	13	71	0.644	69	0.498
High-intermediate, high risk	16	62		41	
Post treatment PET-CT status					
Negative	14	75	0.014	83	<0.001
Positive	14	34		36	

LDH lactate dehydrogenase, OS overall survival, PET-CT positron emission tomography-computed tomography, PFS progression-free survival

However, the positive predictive value of PET-CT is not so high, since judgment of positive uptake is difficult and poor reproducibility of assessment between interpreters

has been pointed out. Although we used the efficacy criteria proposed by Cheson et al., a five-point scale has recently been employed in clinical trials with interim PET and the usefulness of this scale has been reported [17]. Therefore, the criteria for assessing efficacy should be studied further and standardization of the criteria for PET-CT positivity should be a target for the future.

Radiotherapy for residual lesions did not seem to be important in our patients who showed no uptake on post-treatment PET-CT at the end of R-CHOP therapy. However, the present study was not designed to assess the usefulness of radiotherapy, emphasizing the need for additional clinical studies.

In conclusion, the present study demonstrated that a bulky mass was not a poor prognostic indicator for patients with DLBCL. Instead, the results of PET-CT at the end of treatment may be useful for predicting the prognosis. Although our study had the limitations of a retrospective design and a small number of subjects, the results suggested that radiotherapy may not be required for a residual bulky mass if there is no abnormal FDG uptake on PET-CT at the end of R-CHOP therapy. However, confirmation by a prospective study is needed.

Conflict of interest The authors have no conflict of interest to declare.

References

- Shipp MA, Harrington DP, Klatt MM et al (1986) Identification of major prognostic subgroups of patients with large-cell

- lymphoma treated with m-BACOD or M-BACOD. *Ann Intern Med* 104:757–765
2. Hurvich CM, Simonoff JS, Tsai C-L (1998) Smoothing parameter selection in nonparametric regression using an improved Akaike information criterion. *J R Stat Soc* 60:271–293
 3. Fisher RI, DeVita VT Jr, Johnson BL et al (1977) Prognostic factors for advanced diffuse histiocytic lymphoma following treatment with combination chemotherapy. *Am J Med* 63:177–182
 4. Danieu L, Wong G, Koziner B et al (1986) Predictive model for prognosis in advanced diffuse histiocytic lymphoma. *Cancer Res* 46:5372–5379
 5. Hoskins PJ, Ng V, Spinelli JJ et al (1991) Prognostic variables in patients with diffuse large-cell lymphoma treated with MACOP-B. *J Clin Oncol* 9:220–226
 6. Savage KJ, Al Rajhi N, Voss N et al (2006) Favorable outcome of primary mediastinal large B-cell lymphoma in a single institution: the British Columbia experience. *Ann Oncol* 17:123–130
 7. Tomita N, Kodama F, Motomura S et al (2008) Adjuvant radiotherapy to an initial bulky mass in diffuse large B-cell lymphoma: lack of survival benefit. *Int J Lab Hematol* 30:53–57
 8. Habermann TM, Weller EA, Morrison VA et al (2006) Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. *J Clin Oncol* 24:3121–3127
 9. Coiffier B, Lepage E, Briere J et al (2002) CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *New Engl J Med* 346:235–242
 10. Pfreundschuh M, Ho AD, Cavallin-Stahl E, Wolf M, Pettengell R, Vasova I, Belch A, Walewski J, Zinzani PL, Mingrone W et al (2008) Prognostic significance of maximum tumour (bulk) diameter in young patients with good-prognosis diffuse large-B-cell lymphoma treated with CHOP-like chemotherapy with or without rituximab: an exploratory analysis of the MabThera International Trial Group (MInT) study. *Lancet Oncol* 9:435–444
 11. Lister TA, Crowther D, Sutcliffe SB et al (1989) Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: cotswolds meeting. *J Clin Oncol* 7:1630–1636
 12. Takemura S, Tomita N, Koharazawa H et al (2012) Phase II study of CHOP-GR therapy in diffuse large B-cell lymphoma. *Int J Hematol* 96:241–246
 13. Cheson BD, Pfistner B, Juweid ME et al (2007) International harmonization project on lymphoma. Revised response criteria for malignant lymphoma. *J Clin Oncol* 25:579–586
 14. Song MK, Chung JS, Sung-Yong O et al (2010) Clinical impact of bulky mass in the patient with primary extranodal diffuse large B cell lymphoma treated with R-CHOP therapy. *Ann Hematol* 10:985–991
 15. Fukuhara S, Watanabe T, Munakata W et al (2011) Bulky disease has an impact on outcomes in primary diffuse large B-cell lymphoma of the breast: a retrospective analysis at a single institution. *Eur J Hematol* 5:434–440
 16. Juweid ME, Wiseman GA, Vose JM et al (2005) Response assessment of aggressive non-Hodgkin's lymphoma by integrated international workshop criteria and fluorine-18-fluorodeoxyglucose positron emission tomography. *J Clin Oncol* 23:4652–4661
 17. Meignan M, Barrington S, Itti E et al (2014) Report on the 4th international workshop on positron emission tomography in lymphoma held in Menton, France, 3–5 October 2012. *Leuk Lymphoma* 55:31–37