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Serum Albumin Levels Strongly Predict Survival Outcome of Elderly Patients with Diffuse Large B-Cell Lymphoma Treated with Rituximab-Combined Chemotherapy

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ABSTRACT

Background: In the current Japanese aging society, a high number of very elderly patients (age ranged from 80 to 93) with diffuse large B-cell lymphoma (DLBCL, most frequent hematological malignancy), who require chemotherapy are encountered. However, standard chemotherapy can result in severe adverse effects in elderly patients. Although various scoring systems are available to assess frailty, they are too complicated to immediately make a therapeutic decision, and studies on indications for chemotherapy in elderly patients are few.

Materials and Methods: In the present study, we retrospectively analyzed the clinical records of 56 patients with DLBCL aged 80 or older who received R-CHOP or similar chemotherapy. Association of various clinical parameters, including performance status, stage, B symptom(s), laboratory data and relative dose intensity and survival outcomes was examined.

Results: Pretreatment serum albumin level was identified as the only factor that predicts overall and progression-free survivals.

Conclusion: We have concluded that very elderly DLBCL patients aged 80 or older with hypoalbuminemia may be unfit for standard chemotherapy, regardless of other factors. Alternative or palliative therapy should be considered for those patients.

Keywords: Diffuse large B-cell lymphoma; Elderly; Rituximab combined cyclophosphamide; Doxorubicin; Vincristine and prednisolone (R-CHOP); Albumin

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma. Addition of the anti-CD20 antibody rituximab (R) to standard chemotherapy has markedly improved the survival outcome of DLBCL[1]. In Japan's rapidly aging society, the number of patients with DLBCL has been increasing similar to other malignancies. Whereas a

greater part of proportion of younger patients with DLBCL are cured in R era, similar treatment in elderly patients remains unsatisfactory. Only a minor portion of elderly patients with DLBCL, especially of those aged 80 or over, can receive standard chemotherapy due to various comorbidities or frailty[2]. Even in elderly patients who are deemed fit to receive R-combined chemotherapy, some experience therapeutic failure due to severe adverse events, including infection or organ failure. To appropriately indicate R-combined chemotherapy for elderly patients aged 80 or older, exclusion of frail patients using the Charlson comorbidity index (CCI)[3] is proposed[4,5]. Miura et al.[6] also combined CCI with serum albumin measurements to predict prognosis and cytotoxic therapy tolerability. CCI, comprehensive geriatric assessment (CGA)[7], and instrumental activities of daily living (iADL)[8] are known to be useful to assess frailty. However, they are complicated for daily use because they include many items, i. e., cardiovascular, respiratory, renal or digestive function, dementia, diabetes or patients' daily activities. Hematological physicians appear to commonly suffer from difficulty to indicate R-CHOP chemotherapy consisting of rituximab of 375mg/sq on day 1 and 750mg/sq of cyclophosphamide, 50mg/sq of doxorubicin and 1.4mg/sq of vincristine on day 2 and 100mg/body of oral prednisolone through days 2 to 6[1]or similar regimen R-THP-COP consisting of rituximab of 375mg/sq on day 1 and 750mg/sq of cyclophosphamide, 50mg/sq of epirubicin and 1.4mg/sq of vincristine on day 2 and 100mg/body of oral prednisolone through days 2 to 6[9] in elderly patients with DLBCL aged 80 years or older[4,5].To quickly and simply evaluate patients' fitness, we retrospectively analyzed the relationship between various clinical parameters and therapeutic outcomes.

MATERIALS AND METHODS

Patients

Institutional approval in accordance with the Declaration of Helsinki was acquired to retrospectively analyze clinical records of 282 patients with DLBCL treated with chemotherapy between April 2003 and March 2019 (Approval code 2019-1 Aiseikai Yamashina Hospital Review Board). Histological diagnosis was acquired from biopsied specimen gathered at Aiseikai Yamashina Hospital, Japanese Red Cross Kyoto Daiichi Hospital and Kyoto Prefectural University of Medicine according to the World Health Organization classification[10]. Exclusion criteria were as follows: Patients who received radiochemotherapy, primary central nervous system DLBCL for which R-CHOP or a similar regimen would not be effective, cardiac dysfunction with ejection fraction less than 50% on ultrasound cardiography, decompensated hepatic failure and renal impairment with serum creatinine greater than 3 mg/dL. Among 282 patients, 56 were aged 80 years or older and proved not to meet exclusion criteria. Written informed consent was acquired from all patients. A total of 56 patients (27 males and 29 females aged 80 to 93 years with a median of 83.5 years) were evaluated by CCI and their characteristics are summarized in Table 1.

Treatment

All 56 patients were intended to be treated with six cycles of R-CHOP or R-THP-COP. The choice of the chemotherapy regimen, dose reduction and length of chemotherapy interval were decided at the physicians' discretion. The dose of rituximab was conventional in all patients (375mg/sq).

Statistical analyses

Overall survival time (OS) was calculated from the initiation of therapy to the last follow-up or death from any cause. Progression-free survival (PFS) was defined as time to first relapse of the remitted lesion, growth of the refractory disease or death. Using SPSS version 22.0, OS and PFS were assessed by Kaplan-Meier method. The differences in survival outcomes between the following clinical parameters at diagnosis as follows were compared by log-rank test: clinical stage, performance status (PS), serum lactate dehydrogenase (LDH), extranodal lesions, serum albumin (Alb) and C-reactive protein (CRP) appearing in the International Prognostic Index (IPI)[11] and the National Comprehensive Cancer Network (NCCN)-IPI[12], serum soluble interleukin-2 receptor (sIL-2R) and CCI score. Optimal cut-off values of LDH, Alb, CRP and sIL-2R were determined by receiver operator characteristic curve analysis using EZR[13] (Table 1). Parameters with $p < 0.05$ were considered

significant and were evaluated on multivariate analysis by Cox regression test.

Table 1. Patients' characteristics

Age	Range 80–93	Median 83.5
Gender	Male / Female	27 (48.2%) / 29 (51.8%)
Stage	I・II / III・IV	9 (16.1%)・19 (33.9%) / 9 (16.1%)・19 (33.9%)
B symptom	− / +	14 (25%) /42 (75%)
PS	0・1 / 2・3・4	28 (50%)・15 (30%) / 8 (14.3%)・3 (5.4%)・2 (3.6%)
Extranodal lesion	0 or 1 / ≥2	46 (82.1%) / 10 (17.9%)
LDH < 429IU/L	Yes / No	25 (44.6%) / 31 (55.4%)
sIL-2R < 1080U/mL	Yes / No	10 (17.9%) / 46 (82.1%)
Alb > 3.4g/dL	Yes / No	37 (66.1%) / 19 (33.9%)
CRP < 1.5mg/dL	Yes / No	34 (60.7%) / 22 (39.3%)
IPI risk group	L・L-I / H-I・H	24 (42.9%) / 32 (57.1%)
Treatment	R-CHOP / R-THP-COP	41 (73.2%) / 15 (26.8%)
Histological subtype	GCB / ABC / not defined	4 (7.1%) / 18 (32.1%) / 34 (60.7%)
CCI	Score 2・3 / 4・5・6	35 (62.5%)・10 (17.9%) / 9 (16.1%)・1 (1.8%)・1 (1.8%)

PS: performance status, LDH: lactate dehydrogenase, sIL-2R: soluble interleukin-2 receptor, Alb: albumin, CRP: C-reactive protein, IPI: International Prognostic Index, L: Low, L-I: Low-intermediate, H-I: High-intermediate, H: High, GCB: germinal center cell-type, ABC: activated B-cell-type, CCI: Charlson comorbidity index

RESULTS

Only a few patients had a PS of 3 or 4, suggesting that most patients with poor PS were initially regarded as unfit to systemic chemotherapy by attending physicians. Forty-one patients (73.2%) received R-CHOP and the remaining 15 (26.8%) R-THP-COP as the first-line therapy. Dose reduction was indicated in 32 patients (57.1%) and additional dose reduction during the therapeutic schedule in 8 (14.3%), resulting in a median reduction rate of 20% (range 20-50%). Elongation of chemotherapy interval occurred in 31 (55.4%) patients, mainly due to delayed bone marrow recovery. The most common chemotherapy interval was 28 days, whereas 21 days was commonly recommended. Thus, reduction of relative dose intensity (RDI) was experienced by 43 of 56 patients (76.8%), corresponding to more than three-fourths of the patients. It should be noted we did not examine the number of chemotherapy cycles as related to patients' survival time, as short survival due to rapid progression of DLBCL or severe adverse events prevent completion of therapy.

Response to treatment was evaluated according to the criteria using positron emission tomography-computed tomography (PET-CT)[14] in 44 patients (78.6%) and without using PET-CT in the remaining 12[15]. Complete remission (CR), disappearance of the lesions or tumor-related symptoms, was achieved in 40 patients (71.4%) and partial remission (PR), decrease of the lesions 50% or more, in 11 (19.6%), resulting in an overall response (CR + PR) rate of 91.1% (Table 2). The most frequent adverse event was febrile neutropenia, resulting in therapy-related death in two cases (Table 2). It is also notable that secondary malignancy was observed in two patients; lung adenocarcinoma and colon cancer were diagnosed after 60 and 72 months, respectively (Table 2).

Observation periods ranged from 2 to 123 months with a median of 30. OS and PFS rates of all patients were 73.1% and 59.6%, respectively (Fig. 1). IPI and NCCN-IPI depicted significant differences of survival between groups classified as high or high-intermediate risk and low-intermediate or low: OS and PFS were 84.9% vs 59.0% (p value = 0.012) and 74.2% vs 42.4% (p = 0.032) by IPI, respectively, and 100% vs 65.4% (p = 0.020) and 91.7% vs 50.1% (p =

0.032) by NCCN-IPI, respectively. These results suggest that our patients showed no deviated characteristics that affect the survival impact of various parameters. Univariate analyses revealed that the presence of B symptom, a PS of 2 or more, low Alb, elevated LDH and a CCI score of 4 or more were significantly correlated with poor OS and PFS (Table 3). Elevated CRP was an adverse factor in predicting OS (Table 3). Multivariate analysis with PS, B symptom, LDH, Alb, CRP and the CCI for OS and that with PS, B symptom, Alb and the CCI for PFS determined that low serum Alb was the only adverse prognostic factor (Fig. 2, Table 4). Major causes of poor prognosis in hypoalbuminemia group were relapse (12 of 19, 63.2%) and therapy-related deaths from sepsis and heart failure (2 of 19, 10.5%).

Table 2. Therapeutic outcomes

Numbers of chemotherapy cycle 6 / 5 / 4 / 3 / 2 / 1	**46 (82.1%) / 1 (1.8%) / 2 (3.6%) / 3 (5.4%) / 1 (1.8%) / 3 (5.4%)**
Dose reduction rate 0% / 20% / 40% / 50%	24 (42.9%)/21 (37.5%)/10 (17.9%)/1 (1.8%)
Interval of chemotherapy 21 Days / 28 Days / More	25 (44.6%)/29 (51.8%)/2 (3.6%)
Relative dose intensity 1 / 0.8 / 0.75 / 0.6 / 0.5 / 0.45 / 0.4	13 (23.2%) / 8 (14.3%) / 13 (23.2%) / 14 (25%) / 1 (1.8%) / 5 (8.9%) / 2 (3.6%)
Response	
CR	40 (71.4%)
PR	11 (19.6%)
ORR	51 (91.1%)
Adverse events	
FN	35 (62.5%)
Sepsis	1 (1.8%)
Fungal pneumonia	1 (1.8%)
CHF	2 (3.6%)
TRM	2 (3.6%)
Secondary cancer	2 (3.6%) (colon, lung)

CR: complete remission, PR: partial remission, ORR: overall response rate,
FN: febrile neutropenia, CHF: congestive heart failure, TRM: therapy-related mortality

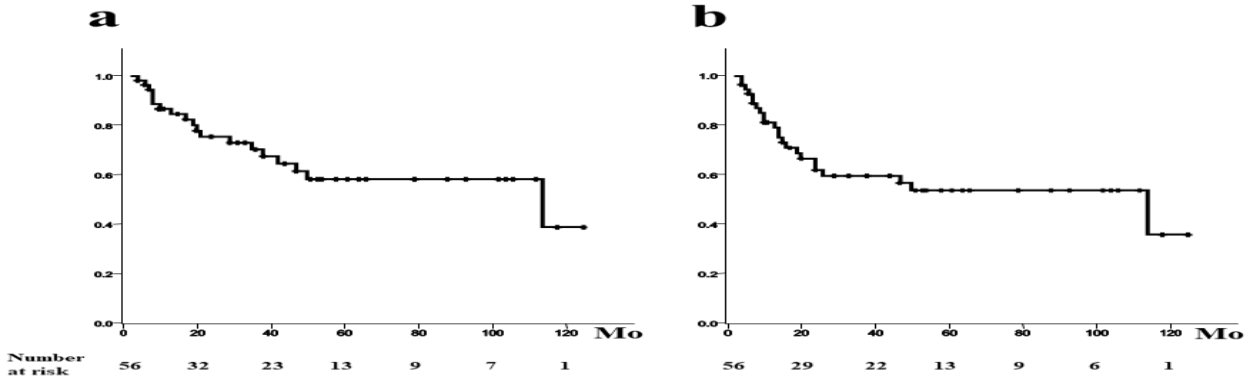

Figure 1. Kaplan-Meier analyses of all 56 patients at a median of 30 months. Overall (a) and progression free (b) survival rates were 73.1% and 59.6%, respectively.

Table 3. Univariate analysis of survival rates at 30 months

Variables		No.	OS	p	PFS	p
Stage	I/II	29	84.1%		68.2%	
				0.077		0.210
	III/IV	27	61.9%		50.5%	
B symptom	-	42	80.6%		67.7%	
				*0.004		*0.029
	+	14	50.0%		33.8%	
PS	0-1	43	86.3%		71.8%	
				*0.000		*0.000
	2-4	13	20.6%		10.6%	
LDH	<429	25	92.0%		829%	
				*0.012		*0.018
	≥429	31	58.5%		41.7%	
Extranodal	<2	46	73.4%		59.2%	
				0.862		0.679
	≥2	10	70.0%		61.7%	
sIL-2R	<1080	10	100%		88.9%	
				0.241		0.309
	≥1080	46	66.8%		53.1%	
Alb	>3.4	37	93.2%		76.2%	
				*0.000		*0.000
	≤3.4	19	25.1%		18.3%	
CRP	<1.5	34	84.4%		69.2%	
				*0.003		0.060
	≥1.5	22	55.1%		45.0%	
RDI	1	13	92.3%		75.2%	
				0.732		0.762
	<1	43	67.7%		55.1%	
CCI	≤3	45	82.1%		67.4%	
				*0.009		*0.021
	≥4	11	38.2%		27.3%	

No.: Numbers of patients, OS: overall survival, PFS: progression-free survival, PS: performance status, LDH: lactate dehydrogenase, SIL-2R: soluble interleukin-2 receptor, Alb: albumin, CRP: C-reactive protein, N: normal, E: elevated. *Significantly different.

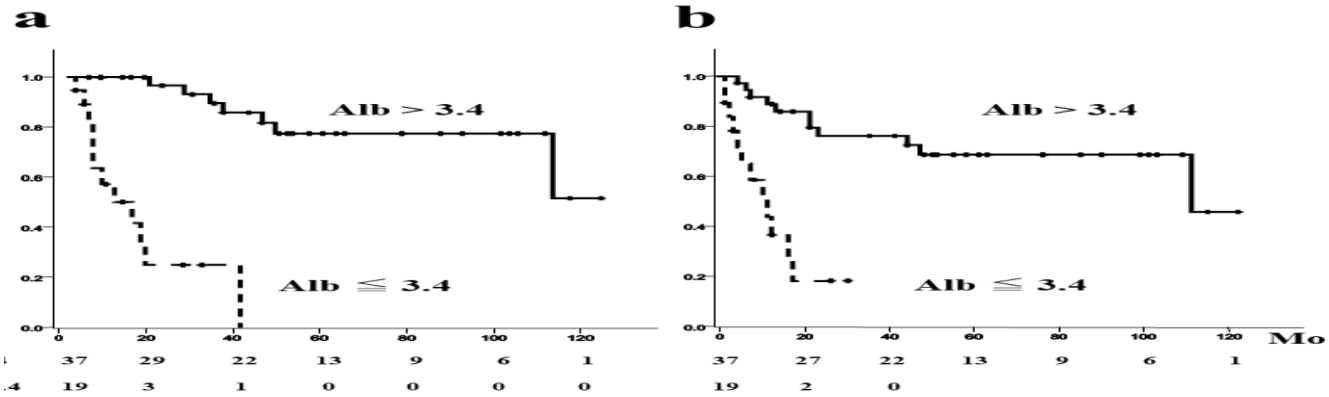

Figure 2. Survival outcomes according to serum albumin level. Both overall (a) and progression free (b) survival rates were significantly superior in the group with serum albumin of greater than 3.4g/dL (93.2% vs 25.1% and 76.2% vs 18.3%, respectively).

Table 4. Multivariate analysis of prognostic factors

Variables	OS			PFS		
	p	HR	95%CI	p	HR	95%CI
B symptom - / +	0.082	0.290	0.072-1.172	0.171	0.434	0.132-1.433
PS 0-1 / 2-4	0.213	2.700	0.566-12.889	0.168	2.681	0.659-10.903
LDH <429 / ≥429	0.636	1.454	0.308-6.857	0.455	1.707	0.420-6.940
Alb >3.4 / ≤3.4	*0.013	14.651	1.774-121.003	*0.035	4.914	1.122-21.518
CRP <1.5 / ≥1.5	0.457	1.536	0.496-4.751	Not examined		
CCI ≤3 / ≥4	0.092	2.797	0.845-9.259	0.264	1.832	0.634-5.296

DISCUSSION

This study was conducted to detect a significant factor that affects therapeutic outcome of elderly patients with DLBCL. We found that pretreatment serum Alb as a sole prognostic factor using multiple clinical characteristics and values. It is often problematic for physicians to determine whether R-CHOP or similar regimen is feasible for elderly DLBCL patients, particularly those aged 80 or older, even if they have sufficient organ function. Chihara et al. described the efficacy of anthracycline, including therapy even for very elderly patients with a median age of 83 years[5]. They emphasized a therapeutic impact of anthracycline. In a controversial study, Laribi et al. reported favorable survival outcomes with R-CVP therapy (Rituximab 375mg/sq on day 1, cyclophosphamide 750mg/sq and vincristine 1.4mg/sq on day 2 and oral prednisolone 100mg/body through days 2 to 6), omitting doxorubicin from R-CHOP[4]. In addition, Iioka et al. recommended a dose-reduced R-CHOP for patients aged 80 or older since the efficacy was not inferior to that of standard R-CHOP[16]. Reduction of severe toxicities was considered to allow a completion of the chemotherapy, offsetting an insufficient RDI. Actually, we failed to demonstrate a survival difference between groups with an RDI at 1.0 or less. Enough RDI appears to cause severe adverse events, negating any therapeutic effect. These emphasize the difficulty in administering standard R-CHOP (like) chemotherapy in some elderly patients, even when the study participants were expected to tolerate systemic chemotherapy. Our present study showed an importance of serum Alb level to predict a fitness to chemotherapy. Unfortunately, existing prognostic indices for DLBCL only indicate the risk of disease relapse or death. Therefore, we propose the use of pretreatment serum Alb levels to more clearly determine whether R-CHOP or similar regimen is applicable for DLBCL patients aged 80 years or older, since we have demonstrated that it is significantly associated with OS and PFS. Although other studies have also reported serum Alb as an important prognostic factor in DLBCL[17-21], it should be noted that the median age of patients included in those studies were younger, and additional factors were also related to survival. A study conducted by Peyrade et al. reported that serum Alb was the single prognostic factor for OS in elderly patients (range of age 80 -95, median 83) with DLBCL who received dose-reductive R-CHOP, called R-miniCHOP[17]. Twelve of 150 patients (8%) included in their study died of therapeutic toxicity in spite of dose reduction with RDI of 0.5. In our study, two patients (3.6%) with reduced RDI died of sepsis as treatment-related mortality (TRM). On the contrary, 24 patients (42.9%) who received full dose administration demonstrated no TRM. Thus, there might be a stronger prognostic factor than RDI. Since serum Alb level is affected by not only nutritional status but also systemic inflammation[22], hypoalbuminemia appears to represent suboptimal frailty for chemotherapy. Elderly patients aged 80 or older with DLBCL who present hypoalbuminemia might had better avoid R-combined chemotherapy. It should be evaluated whether R monotherapy, steroid therapy or best supportive treatment result

in superior prognosis to conventional systemic chemotherapy. The strength of this study was an easy and quick stratification for feasibility of R-combined chemotherapy. However, some limitations should be taken into account since this study was retrospective and contained a small number of elderly patients analyzed.

CONCLUSION

Taken together, DLBCL patients aged 80 years or older who present with hypoalbuminemia (3.4g/dL or lower) should be regarded as unfit for R-CHOP or similar chemotherapy regardless of other factors. Appropriate alternative therapy, i. e., R monotherapy or steroid therapy can be suggested to elderly DLBCL patients with hypoalbuminemia. As this study is not prospective, it contains only a small number of patients and other factors not referred to in our study, i. e., cognitive disorder, depression or social support, have also been documented[23], a larger prospective study should be conducted to confirm our findings.

CONFLICTS OF INTEREST

All authors declare that they have no conflicts of interest.

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