【 ORIGINAL ARTICLE 】

Outcomes in Patients with Classic Hodgkin Lymphoma Treated with ABVD: A Single-center Retrospective Study

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Abstract:
Objective   Classic Hodgkin lymphoma (CHL) has been regarded as a curable disease when treated appropriately, especially in younger patients, and ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) has been regarded as the standard regimen. However, a relatively poor prognosis has been reported in older patients with CHL, and the efficacy and tolerability of the ABVD regimen has not been fully elucidated. We retrospectively investigated the outcomes in patients with CHL treated with ABVD at our institute.
Methods   Twenty-five patients were evaluated; 14 were ≤60 years of age, and 11 were >60 years of age (older group).
Results   The ABVD doses were reduced in all patients in the older group; the median average relative dose intensity was 0.58. In the older group, the 5-year overall survival (OS) and median OS were 100% and not reached, respectively, for patients with early-stage CHL and 66.7% and not reached, respectively, for those with advanced-stage CHL. No patients died of CHL, and only one treatment-related death was observed in the older group.
Conclusion   ABVD with dose attenuation may represent a feasible and effective strategy for the treatment of older patients with CHL in clinical practice, particularly in those with early-stage disease, although the optimal degree of attenuation remains unclear.

Key words: classic Hodgkin lymphoma, older patients, ABVD

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Introduction

Classic Hodgkin lymphoma (CHL) is a heterogeneous group of tumors characterized by the presence of a small number of neoplastic Reed-Sternberg cells on an inflammatory background. In Western countries, CHL is a malignant lymphoma with a high incidence. In Japan, however, CHL accounts for <10% of malignant lymphomas (1). Patients with CHL can be cured with chemotherapy combined with radiation therapy, and ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) has been regarded as the standard

treatment regimen for patients with CHL (2).

A bimodal age distribution has been reported in CHL, with the first peak in younger patients and the second peak in older patients (3). In some studies, about 20% of the patients with Hodgkin lymphoma (HL) were >60 years of age (4-6). The 5-year overall survival (OS) for older patients reportedly ranges from 33% to 65%, and the prognosis for older patients is poor compared with that for younger patients with CHL (7-12). Older patients often have complications, and the administration of chemotherapy at a sufficient dose and on a regular schedule becomes difficult in some cases (13). The efficacy and tolerability of ABVD have not

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been fully elucidated, and the standard treatment has not been established in older patients with CHL.

In this study, we retrospectively investigated the clinical features and outcomes of patients with CHL, including older patients, treated with ABVD at our institute and evaluated the efficacy and feasibility of ABVD in older patients with CHL.

Materials and Methods

Patients

We evaluated patients with CHL at the National Hospital Organization Nagasaki Medical Center (NHO-NMC, Omura, Japan) from November 2003 to December 2016, and those who received ABVD as a first-line treatment were included in this study. Patients with other iatrogenic immunodeficiency-associated lymphoproliferative disorders were not included in this study, even if they had been pathologically diagnosed with CHL. Clinical data were retrospectively collected from the medical records of each patient and updated as of March 2017. We defined Ann Arbor stage IIB with bulky disease, III, and IV as advanced-stage disease and all other classifications as early-stage disease (14).

This retrospective study was approved by the ethics committee and institutional review board of the NHO-NMC, and the procedures followed were in accordance with the Declaration of Helsinki.

Relative dose intensity (RDI)

ABVD consists of doxorubicin (DOX) (25 mg/m^2), bleomycin (BLM) (10 mg/m^2 with an upper-limit dose of 15 mg), vinblastine (VBL) (6 mg/m^2 with an upper-limit dose of 10 mg), and dacarbazine (DTIC) (375 mg/m^2) on days 1 and 15 of each cycle, and 1 cycle takes 4 weeks (2). In some patients, the doses of ABVD were reduced or the timing of administration was postponed based on the judgment of each attending physician. Therefore, we calculated the relative dose intensity (RDI) of each drug in each patient. The dose intensity is defined as the amount of drug delivered to a patient per week of treatment and is used to evaluate the intensity of chemotherapy. The RDI represents the ratio of the amount of a drug actually administered to the amount planned for a fixed time period (15). The average RDI was calculated as the sum of the RDI of DOX, BLM, VBL, and DTIC divided by four.

Treatment response

Response and relapse were defined based on Cheson's criteria (16), and the best response was assessed regardless of the duration of response in this study.

Statistical analyses

Comparisons among the groups were performed using Fisher's exact test as appropriate for categorical variables and the Mann-Whitney U test for continuous variables. The

progression-free survival (PFS) was defined as the time from the initial treatment until death from any cause, relapse, progressive disease, or the day of last follow-up. Patients who were alive at the time of the last follow-up were censored. The OS was defined as the time from initial treatment until death from any cause or the day of last follow-up. Patients who were alive at the time of the last follow-up were censored. The probabilities of a PFS and OS were estimated using the Kaplan-Meier method and compared using the log-rank test. A p value of <0.05 for a two-sided test was considered statistically significant. The 95% confidence intervals (CIs) of the 5-year PFS and OS were calculated.

All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (version 3.4.4; The R Foundation for Statistical Computing, Vienna, Austria). EZR is a modified version of R commander (version 2.4-2), which was designed to add statistical functions that are frequently used in biostatistics (17).

Results

Patients' characteristics

Twenty-six patients were diagnosed with CHL at NHC-NMC during the study period. Among them, one patient was excluded from this study because they had been initially diagnosed with another lymphoma subtype and treated with a regimen other than ABVD. Thus, the remaining 25 patients treated with ABVD as the initial treatment were included in this study. Eleven (44.0%) patients were >60 years of age (older group), and 14 (56.0%) patients were ≤60 years of age (younger group).

The patients' clinical characteristics at the time of the initial treatment in each group are summarized in Table 1. The median age was 73 years old (range, 62-84 years old) in the older group and 31.5 years old (range, 20-59 years old) in the younger group. Five of the 14 (35.7%) patients in the younger group were ≥50 years of age. The clinical stage was early in 7 (63.6%) patients in the older group and in 9 (64.3%) in the younger group. One patient with Ann Arbor stage IIB CHL with bulky disease was included as a patient with advanced-stage disease in the younger group. Two patients in the older group but none in the younger group had an Eastern Cooperative Oncology Group performance status (ECOG PS) of ≥3. There was a significant difference in the histopathological subgroups between the 2 groups (p = 0.004). In the older group, 9 (81.8%) patients were diagnosed with mixed cellularity CHL (MC-CHL) and 2 (18.2%) with lymphocyte-rich CHL (LR-CHL). In the younger group, 8 (57.1%) patients were diagnosed with nodular sclerosis CHL (NS-CHL), 5 (35.7%) with MC-CHL, and 1 (7.1%) with LR-CHL.

All patients were positive for CD30 expression, and there was no significant difference in the CD15 or CD20 expression between the groups. The Epstein-Barr virus (EBV)

Table 1.   Clinical Characteristics at Patients' Initial Treatment.

Characteristics	Older group (n=11) (Age>60 years)		Younger group (n=14) (Age ≤ 60 years)		p value
	No. of patients	%	No. of patients	%	
Age, years					
Median (range)	73 (62-84)		31.5 (20-59)		
Sex					0.70
Male	5	45.5	8	57.1	
Female	6	54.5	6	42.9	
Ann Arbor stage					1.00
Early stage	7	63.6	9	64.3	
IA	1	9.1	0	0	
IB	0	0	0	0	
IIA	4	36.4	7	50.0	
IIB non bulky	2	18.2	2	14.3	
Advanced stage	4	36.4	5	35.7	
IIB bulky	0	0	1	7.1	
IIIA	1	9.1	1	7.1	
IIIB	1	9.1	0	0	
IVA	0	0	0	0	
IVB	2	18.2	3	21.4	
ECOG PS					0.18
≤ 2	9	81.8	14	100	
3, 4	2	18.2	0	0	
Histopathology					0.004
Nodular sclerosis	0	0	8	57.1	
Mixed cellularity	9	81.8	5	35.7	
Lymphocyte-rich	2	18.2	1	7.1	
Lymphoctyte-depleted	0	0	0	0	
CD15					1.00
Positive	5	45.5	6	42.9	
Negative	4	36.4	5	35.7	
Not done	2	18.2	3	21.4	
CD20					0.12
Positive	3	27.3	1	7.1	
Negative	4	36.4	11	78.6	
Not done	4	36.4	2	14.3	
CD30					1.00
Positive	11	100	14	100	
EBV					0.27
Positive	4	36.4	4	28.6	
Negative	3	27.3	8	57.1	
Not done	4	36.4	2	14.3	
Comorbidity	7	63.6	2	14.3	0.02
WBC count (×10⁹/L)					<0.001
Median (range)	5.5 (2.1-8.1)		9.5 (5.2-21.6)		
Lymphocyte count (×10⁹/L)					0.02
Median (range)	0.8 (0.2-2.3)		1.8 (0.5-4.1)		
Hemoglobin level (g/dL)					0.13
Median (range)	12.7 (6.8-14.7)		13.6 (7.8-16.9)		
Serum albumin (g/dL)					0.95
Median (range)	3.9 (2.8-4.9)		4.0 (1.4-5.5)		
Initial treatment					0.05
ABVD without attenuation	0	0	5	35.7	
ABVD with attenuation	11	100	9	64.3	

ECOG PS: Eastern Cooperative Oncology Group performance status, WBC: white blood cell, ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine, EBV: Epstein–Barr virus

Table 2. Prognostic Factors of Patients with (a) Early-stage and (b) Advanced-stage Disease.

Table 2a

Prognostic factor	Older group (n=7) (Age>60 years)		Younger group (n=9) (Age ≤ 60 years)		p value
	No. of patients	%	No. of patients	%	
Large mediastinal mass	1	14.3	4	44.4	0.31
Extranodal involvement	0	0	0	0	1.00
≥ 3 nodal areas involved	3	42.9	5	55.6	1.00
Increased ESR	1	14.3	1	11.1	1.00

ESR: erythrocyte sedimentation rate

Table 2b

Prognostic factor	Older group (n=4) (Age>60 years)		Younger group (n=5) (Age ≤ 60 years)		p value
	No. of patients	%	No. of patients	%	
Serum albumin<4.0 g/dL	3	75.0	5	100	0.44
Hemoglobin level<10.5 g/dL	1	25.0	1	20.0	1.00
Male	3	75.0	2	40.0	0.52
Age ≥ 45 years	4	100	1	20.0	0.048
Ann Arbor stage IV	2	50.0	3	60.0	1.00
WBC count ≥ $15×10^9$/L	0	0	3	60.0	0.17
Lymphocyte count < $0.6 × 10^9$/L or < 8%	1	25.0	3	60.0	0.52

WBC: white blood cell

status was evaluated by the expression of EBV-latent membrane protein or EBV-encoded small RNA *in situ* hybridization. Four patients in the older group (three with MC-CHL and one with LR-CHL) and four patients in the younger group (three with MC-CHL and one with NS-CHL) were positive for EBV.

A significantly higher proportion of patients in the older than younger group had comorbidities (p = 0.02). There were eight comorbidities in seven of 11 patients in the older group: three had hypertension, one had hepatitis B virus infection, one had diabetes, one had a history of cerebral infarction, and one had myelodysplastic syndrome and chronic obstructive pulmonary disease (COPD). Two of 14 patients in the younger group had comorbidities: one had hypertension and one had depression. The comorbidities were well-controlled at the initiation of chemotherapy in all patients.

Laboratory test results showed that the white blood cell count and lymphocyte count were significantly lower in the older than in the younger group (p <0.001 and 0.02, respectively). The proportion of patients with potential poor prognostic factors (14, 18) was not significantly different between the two groups in those with early-stage disease (Table 2a and Supplementary material 1). In the patients with advanced-stage disease, the proportion of those with potential poor prognostic factors other than age (19) was also not significantly different between the two groups (Table 2b).

RDI and response

Table 3 summarizes the RDI and response in both groups. In the older group, a median of 4 (range, 2-6 cycles) and 7 (range, 3-7 cycles) ABVD cycles were administered for early- and advanced-stage disease, respectively (Table 3a). One patient did not receive medication on day 15 of the final cycle (Patient No. 10 in Table 3a). Four patients (Patient Nos. 2, 3, 5, and 7 in Table 3a) discontinued bleomycin during the treatment based on the decision of their attending physician. The reasons for the discontinuation of bleomycin were an older age (n = 3) and COPD (n = 1). After ABVD, two patients with early-stage disease received radiotherapy (Patient Nos. 2 and 6). In the younger group, the median number of ABVD cycles for early- and advanced-stage disease was 5 (range, 2-8 cycles) and 6 (range, 6-8 cycles), respectively (Table 3b). Two patients did not receive medication on day 15 of the final cycle (Patient Nos. 11 and 13 in Table 3b).

Six patients with early-stage disease and two with advanced-stage disease received radiotherapy after ABVD (Patient Nos. 3, 5-10, and 12 in Table 3b). In both groups, radiotherapy was conducted as first-line therapy after ABVD. Reasons for not receiving radiotherapy were an older age (n = 3) and patients' preference (n = 2) in the older group and a larger irradiation field (n = 1) and unknown (n = 2) in the younger group. Attenuation of ABVD was at the discretion of the attending physician and was based on the patient's condition, without any predetermined policy.

The median doses of DOX, BLM, VBL, and DTIC were significantly lower in the older group than in the younger group (p = 0.02, 0.01, 0.02, and 0.02, respectively; Mann-Whitney *U* test). In the older group, the median RDI of DOX, BLM, VBL, and DTIC was 0.70 (range, 0.19-0.91), 0.48 (range, 0.20-0.88), 0.70 (range, 0.08-0.91), and 0.46

Table 3.   Summary of the (a) Older and (b) Younger Group in the Present Study.

Table 3a

No.	Age	Ann Arbor Stage	No. of prognostic factors	Comorbidity	No. of ABVD cycles	DOX	BLM	VBL	DTIC	Average	ABVD followed by RT	Sites of irradiation	Total dose irradiation (Gy)	Best response	Relapse/progression	PFS (months)	Outcome	Follow-up time (months)
Early-stage																		
1	75	IIB	1	Hypertension	6	0.85	0.88	0.85	0.59	0.79	-	-	-	CR	-	108.5	Alive	108.5
2	70	IIA	0	Hypertension	4	0.74	0.60	0.73	0.51	0.64	+	Bilateral cervical LN	30.6	CR	-	141.6	Alive	141.6
3	78	IIB	1	None	6	0.36	0.24	0.40	0.24	0.31	-	-	-	PR	-	92.6	Dead*	92.6
5	67	IIAX	2	HBV carrier	6	0.44	0.42	0.41	0.37	0.41	-	-	-	CR	-	110.2	Dead*	110.2
6	73	IA	0	Diabetes	3	0.91	0.82	0.91	0.61	0.81	+	Right cervical LN	30.6	CR	-	95.0	Alive	95.0
8	79	IIA	0	MDS	4	0.47	0.42	0.47	0.31	0.42	-	-	-	PR	-	60.3	Alive	60.3
10	62	IIA	1	None	2–1	0.75	0.68	0.75	0.50	0.67	-	-	-	CR	+	20.5	Alive	131.1
Advanced-stage																		
4	82	IIIB	4	None	3	0.19	0.42	0.08	0.32	0.25	-	-	-	CR	-	5.6	Alive	5.6
7	70	IIIAE	2	History of cerebral infarction COPD	7	0.71	0.20	0.71	0.71	0.58	-	-	-	CR	+	13.2	Alive	95.6
9	84	IVB	4	Hypertension	7	0.57	0.48	0.57	0.38	0.50	-	-	-	CR	-	11.8	Dead*	11.8
11	64	IVB	4	None	6	0.70	0.63	0.70	0.46	0.62	-	-	-	CR	-	69.6	Alive	69.6

HBV: hepatitis B virus, MDS: myelodysplastic syndrome, COPD: chronic obstructive pulmonary disease, DOX: doxorubicin, BLM: bleomycin, VBL: vinblastine, DTIC: dacarbazine, RDI: relative dose intensity, ABVD: DOX, BLM, VBL, and DTIC, RT: radiotherapy, CR: complete remission, PR: partial remission, PFS: progression-free survival, LN: lymph node

No. of prognostic factors is as follows: the sum of the prognostic factors for German Hodgkin Study Group in patients with early-stage disease (14) and the sum of the prognostic factors for International Prognostic Score in patients with advanced-stage disease (18). *The causes of death were as follows: pneumonia in Patient No. 3, aortic dissection in Patient No. 5, and invasive pulmonary aspergillosis in Patient No. 9.

(range, 0.24-0.71), respectively, and the median average RDI was 0.58 (range, 0.25-0.81). Among those in the older group with early-stage disease who had no poor prognostic factors, the median average RDI was 0.64 (range, 0.42-0.81) (Table 3a). In the younger group, the median RDI of DOX, BLM, VBL, and DTIC was 0.96 (range, 0.77-1.00), 0.87 (range, 0.62-1.00), 0.96 (range, 0.77-1.00), and 0.66 (range, 0.57-1.00), respectively, and the median average RDI was 0.87 (range, 0.75-1.00). Thus, the actual RDI was significantly lower in the older group than in the younger group (p <0.001). The reasons for ABVD attenuation in the older group were an older age (n = 11), poor ECOG PS (n = 2), leukopenia (n = 1), and COPD (n = 1); some patients had more than one reason. The overall response rate to ABVD was 100% in both groups; 9 patients achieved complete remission (CR), and 2 achieved partial remission (PR) in the older group, and 11 patients achieved CR and 3 achieved PR in the younger group.

Survival analyses

The median follow-up time for the survivors was 69.5 months (range, 5.6-141.6 months) for all patients. The 5-year and median PFS in patients with early-stage disease were 92.9% (95% CI, 59.1-99.0%) and not reached [95%

CI, 7.6 years-not evaluated (NE)], respectively, and those in patients with advanced-stage disease were 42.9% (95% CI, 9.8-73.4%) and 1.2 years (95% CI, 1.0 year-NE), respectively (Fig. 1a). The 5-year and median OS in patients with early-stage disease were 100% and not reached (95% CI, 7.6 years-NE), respectively, and those in patients with advanced-stage disease were 85.7% (95% CI, 33.4-97.9%) and not reached (95% CI, 0.9 years-NE), respectively (Fig. 1b). The PFS was significantly worse in patients with advanced-stage disease than in those with early-stage disease.

In the analysis of patients with early-stage disease by age groups, the 5-year and median PFS in the older group were 85.7% (95% CI, 33.4-97.9%) and 9.1 years (95% CI, 1.7 years-NE), respectively, and those in the younger group were 100% and not reached, respectively (Fig. 2a). The 5-year and median OS in the older group were 100% and not reached (95% CI, 7.6 years-NE), respectively, and those in the younger group were 100% and not reached, respectively (Fig. 2b). The patients in the older group with early-stage disease without any poor prognostic factors had no relapse of CHL and were alive without progression during the observation period (median PFS, 95.0 months; range, 60.3-141.6 months). In patients with advanced-stage disease, the

Table 3. Summary of the (a) Older and (b) Younger Group in the Present Study. (Continued)

Table 3b

No.	Age	Ann Arbor Stage	No. of prognostic factors	Comorbidity	No. of ABVD cycles	DOX	BLM	VBL	DTIC	Average	ABVD followed by RT	Sites of irradiation	Total dose irradiation (Gy)	Best response	Relapse/ progression	PFS (months)	Outcome	Follow-up time (months)
Early-stage																		
2	52	IIB	2	None	6	0.95	0.99	0.95	0.66	0.89	-	-	-	CR	-	126.2	Alive	126.2
3	50	IIA	0	Hypertension	4	1.00	1.00	1.00	1.00	1.00	+	Right cervical LN	30.6	CR	-	46.0	Alive	46.0
5	22	IIAX	1	None	6	0.92	0.62	0.92	0.61	0.77	+	Mediastinal mass	30.6	PR	-	69.4	Alive	69.4
6	32	IIA	1	Depression	4	0.94	0.85	0.94	0.63	0.84	+	Bilateral cervical LN	32.4	CR	-	47.4	Alive	47.4
7	41	IIAX	1	None	5	0.95	0.95	0.95	0.63	0.87	+	Mediastinal mass	39.6	CR	-	87.7	Alive	87.7
9	29	IIAX	2	None	2	0.98	0.88	0.98	0.65	0.88	+	Right cervical LN	39.6	CR	-	70.3	Alive	70.3
11	59	IIB	0	None	8-1	0.96	0.75	0.96	0.64	0.83	-	-	-	CR	-	17.7	Alive	17.7
12	50	IIA	1	None	2	1.00	1.00	1.00	1.00	1.00	+	Left cervical LN	20.0	CR	-	23.7	Alive	23.7
14	20	IIAX	2	None	6	0.77	0.70	0.77	0.77	0.75	-	-	-	CR	-	7.4	Alive	7.4
Advanced-stage																		
1	27	IIBX	4	None	6	0.97	0.89	0.97	0.66	0.88	-	-	-	PR	+	14.0	Alive	26.9
4	31	IIIA	3	None	6	0.86	0.77	0.86	0.57	0.76	-	-	-	CR	-	91.2	Alive	91.2
8	27	IVBX	5	None	8	0.97	0.65	0.97	0.64	0.81	+	Mediastinal mass	36.0	CR	-	83.3	Alive	83.3
10	20	IVBX	3	None	8	0.97	0.72	0.97	0.97	0.91	+	Right cervical LN	40.0	PR	+	13.3	Alive	38.1
13	50	IVB	3	None	6-1	1.00	0.90	1.00	1.00	0.98	-	-	-	CR	-	11.2	Alive	11.2

5-year and median PFS in the older group were 33.3% (95% CI, 0.9-77.4%) and 1.1 years (95% CI, 1.0 year-NE), respectively, and those in the younger group were 50.0% (95% CI, 5.8-84.5%) and 1.2 years (95% CI, 1.1 years-NE), respectively (Fig. 3a). The 5-year and median OS in the older group were 66.7% (95% CI, 5.4-94.5%) and not reached (95% CI, 1.0 year-NE), respectively, and those in the younger group were 100% and not reached, respectively (Fig. 3b).

Two patients in the older group developed relapse. One patient with advanced-stage disease developed relapse 13 months after the initial treatment and was treated with C-MOPP (cyclophosphamide, vincristine, procarbazine, and prednisone)hyou (20) as salvage chemotherapy (Patient No. 7 in Table 3a). This patient subsequently achieved CR again. The other patient with early-stage disease developed relapse 21 months after the initial treatment and was treated with ABVD with attenuation followed by radiotherapy as salvage chemotherapy (Patient No. 10 in Table 3a). This patient also subsequently achieved CR again.

Three patients (two with early-stage disease and one with advanced-stage disease) died during the observation period; all were in the older group. The cause of death and the day of death after the last chemotherapy session were invasive pulmonary aspergillosis on day 34 (Patient No. 9 in Table 3a), pneumonia on day 2,524 (Patient No. 3 in Ta-

ble 3a), and aortic dissection on day 3,082 (Patient No. 5 in Table 3a), respectively. No patients died of CHL. No significant differences in the PFS or OS were observed with respect to the potential prognostic factors in the univariate analysis, such as a large mediastinal mass, erythrocyte sedimentation rate, and number of involved nodal areas in patients with early-stage disease and the serum albumin level, hemoglobin level, sex, age, Ann Arbor stage, white blood cell count, and lymphocyte count in patients with advanced-stage disease (data not shown).

Toxicity

Grade ≥3 adverse events are summarized in Table 4. There were no statistically significant differences other than in the rate of leukopenia between the two groups, but most of the adverse events were reported more frequently in the older group than in the younger group. Hematological adverse events were the most frequent. Leukopenia, neutropenia, and lymphopenia occurred in 90.9%, 81.8%, and 45.5% of patients in the older group, respectively, and in 42.9%, 42.9%, and 21.4% of patients in the younger group, respectively. Anemia, thrombocytopenia, and febrile neutropenia occurred in 9.1%, 9.1%, and 18.2% of patients in the older group, respectively, and in 14.3%, 7.1%, and 0.0% of patients in the younger group, respectively. Although few non-hematological severe adverse events occurred, secondary
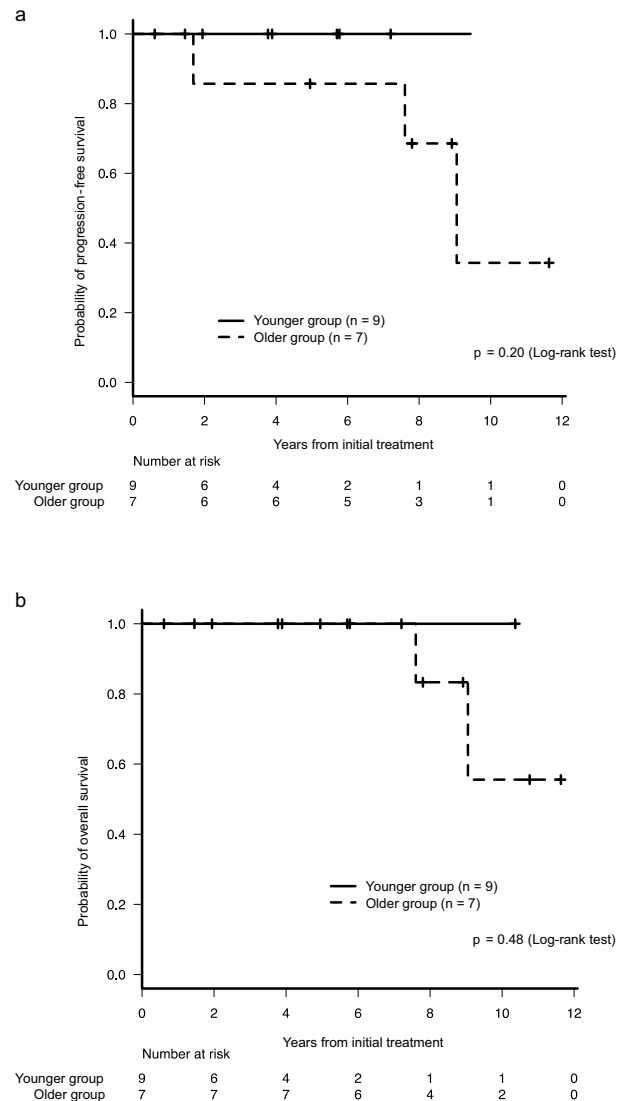
a

b
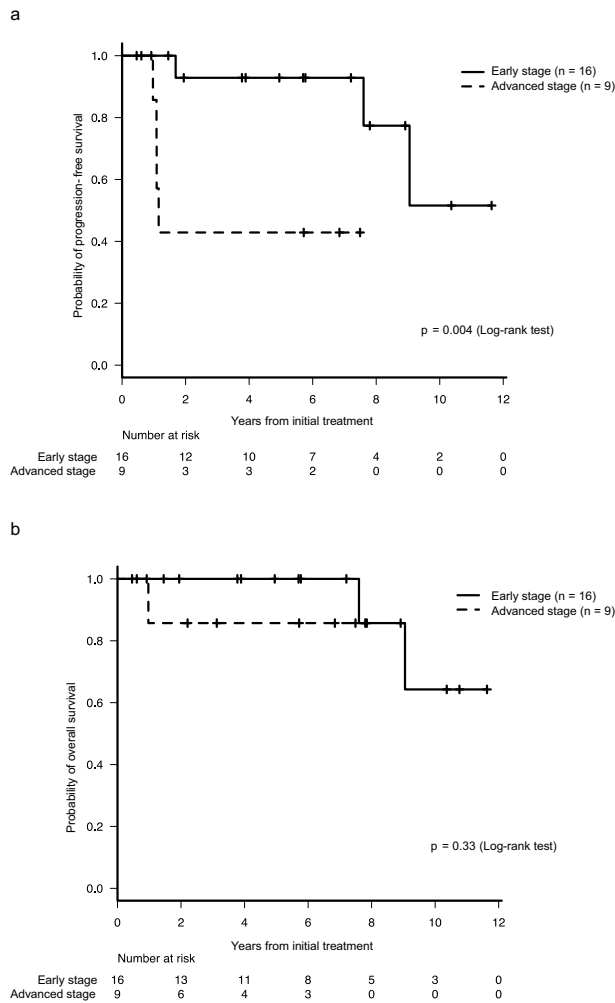
Figure 1. Kaplan-Meier estimates of the probability of a (a) progression-free survival and (b) overall survival of patients with classic Hodgkin lymphoma.

a

b

Figure 2. Kaplan-Meier estimates of the probability of a (a) progression-free survival and (b) overall survival of patients with early-stage classic Hodgkin lymphoma between the younger group and older group.

malignancies were observed only in the older group (one report of breast cancer and one report of prostate cancer).

Discussion

We evaluated the outcomes in patients with CHL who were treated at a single institute in this study. The median age at the diagnosis was 52 years old (range, 20-84 years old), and the proportion of older patients (>60 years old) was 44%. The median age at the diagnosis for patients with CHL is reportedly 41.3 years old (range, 26.8-63.5 years old) in Western countries (21) and 34 years old (range, 14-83 years old) in Japan (22). Thus, the patients with CHL in our study were older than those in previous reports. The proportion of older patients will increase as the population ages over time, and the treatment strategy for older patients will become more important in future.

Although several clinical trials have been conducted in older patients with CHL (23-26), no regimen has been shown to provide a better clinical outcome than ABVD. Therefore, ABVD has been widely regarded as the standard treatment for older patients with CHL, largely based on the

experience in younger patients. However, ABVD might not be appropriate for many older patients, and dose attenuation might be required to reduce toxicities. In the present study, although the doses of ABVD were reduced and the treatment interval was extended in most of the older patients, hematological adverse events such as leukopenia, neutropenia, and lymphopenia were frequently observed. In addition, febrile neutropenia was observed in two patients, and grade ≥3 infection was observed in one patient in the older group. Thus, careful management is recommended in the treatment of older patients with the ABVD regimen, even with attenuated intensity. BLM-modified ABVD has been used to treat older patients with CHL in an attempt to attenuate the ABVD intensity, and this might be an option for reducing the pulmonary toxicity (27). In the present study, the median RDI of BLM for the patients in the older group was low, which might have been a factor in there being no deaths from BLM-induced interstitial pneumonia.

The reduced RDI has been suggested as an important cause of the worse outcome in older patients with CHL. An average RDI of ≥80% was achieved in only 59% of the

older patients with HL in a previous study (23). In the present study, the average RDI was even lower than that in the previous study; however, the outcome was better than expected in the older group, especially among patients with early-stage disease. The difference in the patients' backgrounds might have been associated with the better outcome in our study. The ECOG PS was ≤2 in most of the patients (81.8%), and few patients with potential poor prognostic factors other than age were included in the older group (Table 2). Serious comorbidities were found in more than half of the patients with CHL in a previous report (28). In the present study, however, 7 patients (63.6%) in the older group had comorbidities, but those with serious comorbidities were not included.

The cause of death among older patients has previously been reported as CHL in 18% to 54%, treatment-related toxicity in 8% to 42%, and secondary malignancy in approximately 15% of those who died (4, 9, 23, 27). In the present study, three older patients (Patient Nos. 3, 5, and 9 in Table 3a) died during the observation period, and the causes of death were pneumonia (Patient No. 3), aortic dissection (Patient No. 5), and invasive pulmonary aspergillosis (Patient No. 9).

The observation time was short in one patient (Patient No. 9), and relapse may not have been observed due to competitive risk. The PFS was relatively long in two other patients (Patient Nos. 3 and 5). The results of this study suggest the efficacy of attenuated treatment for older patients. For early-stage patients without poor prognostic factors, clinical guidelines allow for attenuation in the treatment of CHL (29). Prognostic factors and comorbidities should be carefully evaluated in older patients with CHL, and further studies are needed to establish the appropriate degree of attenuation during treatment.

Several limitations associated with the present study warrant mention. First, it was a single-center retrospective study with a small number of patients, and selection bias might have existed. Second, in ABVD with attenuated intensity, the doses and treatment intervals were modified by the attending physicians; there was no standardized procedure.
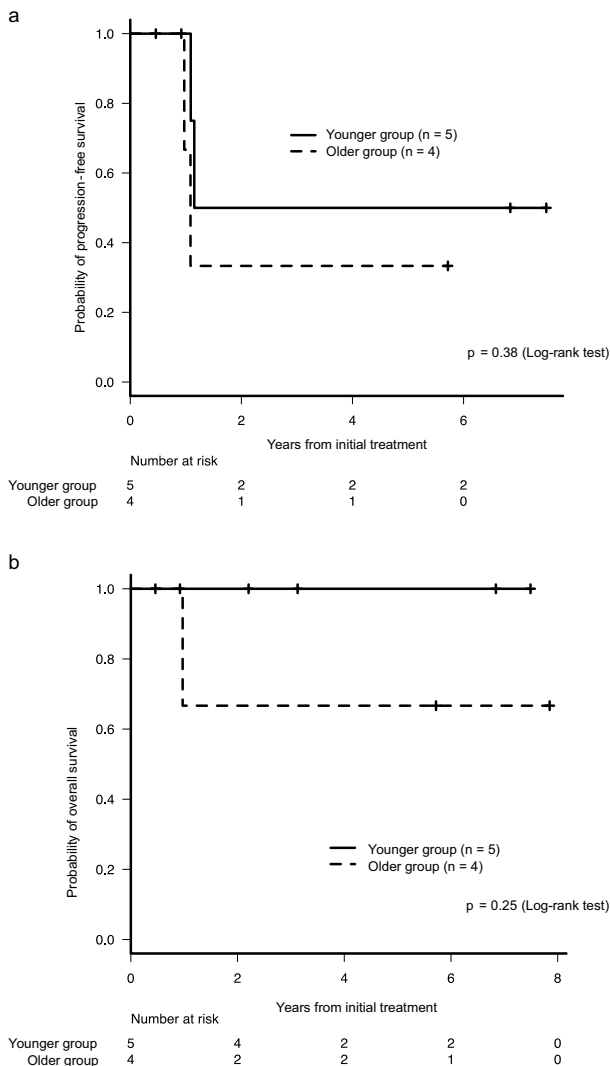
Figure 3. **Kaplan-Meier estimates of the probability of a (a) progression-free survival and (b) overall survival of patients with advanced-stage classic Hodgkin lymphoma between the younger group and older group.**

Table 4. **Grade ≥3 Adverse Events.**

Adverse events	Older group (n=11) (Age>60 years)		Younger group (n=14) (Age ≤ 60 years)		p value
	No. of patients	%	No. of patients	%	
Hematological					
Leukopenia	10	90.9	6	42.9	0.03
Neutropenia	9	81.8	6	42.9	0.10
Lymphopenia	5	45.5	3	21.4	0.39
Anemia	1	9.1	2	14.3	1.00
Thrombocytopenia	1	9.1	1	7.1	1.00
Febrile neutropenia	2	18.2	0	0	0.18
Non-hematological					
Infection	1	9.1	1	7.1	1.00
Secondary malignancy	2	18.2	0	0	0.18

Thus, no conclusions regarding attenuation, such as the recommended dose and treatment interval, could be drawn in the present study. However, our study showed the outcome in older patients with CHL treated with ABVD using an attenuated intensity, and the results support the efficacy and safety of this regimen in clinical practice.

In summary, ABVD with attenuation appears to represent a feasible and effective approach to the treatment of CHL in older patients in clinical practice, especially for those with early-stage disease without any poor prognostic factors. Our results might be helpful for considering treatment options for those patients.

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