tice. Further study of the utility of these biological tools is necessary to improve diagnosis and management of this disease.

In conclusion, the present study demonstrated that IPI and the presence of pleural or pericardial effusion were adverse prognostic factors for risk stratification of PMBL patients treated with R-CHOP. R-CHOP without consolidative RT can achieve a high rate of cure for approximately one-half of PMBL patients, while alternative regimens, including DA-EPOCH-R, should be offered to the remaining patients. Prospective studies to validate these prognostic factors and a risk-adopted treatment strategy are warranted.

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RESEARCH ARTICLE

The role of hematopoietic stem cell transplantation for relapsed and refractory Hodgkin lymphoma

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The optimal treatment strategy with the use of hematopoietic stem cell transplantation (HSCT) for relapsed and refractory Hodgkin lymphoma (HL) remains unclear. We performed a retrospective analysis using registry data from the Japanese Society for Hematopoietic Cell Transplantation. Adult patients with HL who underwent a first autologous or a first allogeneic HSCT between 2002 and 2009 were included. Patients who underwent HSCT in first complete remission (CR) were excluded. Autologous and allogeneic HSCT were performed in 298 and 122 patients, respectively. For autologous HSCT, overall survival at 3 years (3yOS) was 70%, and sex, age, disease status, and performance status (PS) at HSCT were prognostic factors. OS was favorable even in patients who underwent autologous HSCT in disease status other than CR. For allogeneic HSCT, 3yOS was 43%, and sex and PS at HSCT were prognostic factors. Disease status at HSCT, previous autologous HSCT, and conditioning intensity did not affect OS. Moreover, graft-versus-host disease did not affect progression-free survival or relapse/progression rate. A first allogeneic HSCT without a previous autologous HSCT was performed in 40 patients. 3yOS was 45%, and was significantly inferior to that in patients who underwent their first autologous HSCT. This result was retained after the correction by the different patient characteristics according to the type of HSCT. In conclusion, autologous HSCT is effective in prolonging survival in patients with relapsed and refractory HL. Allogeneic HSCT might be beneficial even to relapsed HL after autologous HSCT, although establishing the role of allogeneic HSCT remains a challenge.
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Introduction

Most patients with Hodgkin lymphoma (HL) can expect to be cured with standard chemotherapy with or without radiotherapy. However, 2–5% and 5–10% of patients have a primary refractory disease, and 10–15% and 25–30% of patients experience relapse after conventional chemotherapy in early-stage HL and advanced-stage HL, respectively [1,2]. For these patients, several studies have demonstrated that autologous hematopoietic stem cell transplantation (HSCT) can prolong survival [3–5]. In a randomized trial, Schmitz *et al.* reported longer time to treatment failure in patients with chemosensitive relapsed HL who underwent autologous HSCT, compared to those who underwent only conventional chemotherapy [5]. However, the optimal treatment strategy for chemoresistant HL has not been established, and the role of allogeneic HSCT for HL remains unclear [6]. Therefore, we performed a retrospective analysis using registry data from the Japanese Society for Hematopoietic Cell Transplantation (JSHCT) to clarify the roles of both autologous and allogeneic HSCT for relapsed and refractory HL.

Methods

Data source. Patients with HL aged more than 15 years who underwent a first autologous or a first allogeneic HSCT between 2002 and 2009 were included in this study. Clinical data for these patients were obtained from the Transplant Registry Unified Management Program (TRUMP) [7], which is the registry data of the JSHCT. We excluded patients who underwent HSCT in first complete remission (CR), since previous randomized studies have not supported the benefit of HSCT in first CR [8,9]. This study was planned by the Adult Lymphoma Working Group of JSHCT, and was approved by the data management committee of TRUMP and by the institutional review board of Nagoya University School of Medicine.

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Conflict of interest: Nothing to report

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TABLE I. Patient Characteristics

		Autologous HSCT (n = 298)	Allogeneic HSCT (n = 122)
Patient characteristics at diagnosis			
Sex	Male	200 (67%)	80 (66%)
	Female	98 (33%)	42 (34%)
Clinical stage at diagnosis	1	15 (5%)	3 (2%)
	2	115 (39%)	42 (34%)
	3	83 (28%)	29 (24%)
	4	83 (28%)	44 (36%)
B symptoms at diagnosis	−	176 (59%)	52 (43%)
	+	116 (39%)	61 (50%)
Previous autologous HSCT	−		40 (33%)
	+		82 (67%)
Patient characteristics at HSCT			
	Median follow-up days for survivors (range) [days after HSCT]	935 (14–3094)	948 (104–3214)
	Median age at HSCT (range) [year]	34 (16–75)	31 (16–68)
	Median duration between diagnosis and HSCT (range) [days]	672 (48–6313)	899 (77–5106)
Disease status at HSCT	CR	103 (35%)	24 (20%)
	PR	76 (25%)	16 (13%)
	other status	119 (40%)	82 (67%)
PS at HSCT	0	180 (60%)	51 (42%)
	1	97 (33%)	47 (39%)
	2	15 (5%)	9 (7%)
	3	2 (1%)	4 (3%)
	4	1 (1%)	3 (2%)
Stem cell source	BM	2 (1%)	56 (46%)
	PB	295 (98%)	53 (43%)
	BM+PB	1 (1%)	1 (1%)
	CB	-	11 (9%)
Donor relationship	MR		47 (39%)
	MMR		20 (16%)
	MUR		21 (17%)
	MMUR		19 (16%)
	CB		11 (9%)
Conditioning regimen including TBI	−	278 (93%)	57 (47%)
	+	8 (3%)	61 (50%)
Intensity of conditioning regimen	MAC		37 (30%)
	RIC		76 (62%)

HSCT, hematopoietic stem cell transplantation; CR, complete remission; PR, partial remission; PS, performance status; BM, bone marrow; PB, peripheral blood; CB, cord blood; MR, human leukocyte antigen (HLA)-matched related; MMR, HLA-mismatched related; MUR, HLA-matched unrelated; MMUR, HLA-mismatched unrelated; TBI, total body irradiation; MAC, myeloablative conditioning; RIC, reduced-intensity conditioning.

Statistical considerations. Differences between groups were examined using Fisher's exact test for categorical variables. Overall survival (OS) and progression-free survival (PFS) were calculated using the Kaplan–Meier method, whereas the relapse/progression rate (RR) and non-relapse/progression mortality (NRM) were calculated using Gray's method considering each other event as a competing risk [10].

To evaluate the influence of factors for OS, proportional-hazards modeling was used for univariate and multivariate analyses. Factors with a P value of <0.10 in univariate analyses were subjected to multivariate analyses using the backward stepwise selection of covariates. Finally, P values of <0.05 were considered statistically significant. Different patients' characteristics according to the type of HSCT that patients underwent as their first HSCT were considered with Fisher's exact test in univariate analyses and a logistic regression analysis using the backward stepwise selection of covariates in multivariate analyses.

All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University) [11], which is a graphical user interface for R (The R Foundation for Statistical Computing, version 2.13.0, Vienna, Austria).

Results

Patient characteristics

Two hundred ninety-eight patients who underwent their first autologous HSCT and 122 patients who underwent their first allogeneic HSCT were included in this study. Eighty-two of the 122 patients (67%) who underwent their first allogeneic HSCT had previously received autologous HSCT, including seven patients who had a planned allogeneic HSCT following autologous HSCT. The characteristics of the patients are summarized in Table I.

Outcome of a first autologous HSCT

With a median follow-up time from HSCT of 935 days (range: 14–3094 days) for survivors, OS from HSCT in the 298 patients who underwent autologous HSCT was 85% at 1 year and 70% at 3 years (Fig. 1A). Through the univariate and multivariate analyses, female, younger age, disease status of CR, and better performance status (PS) at HSCT were significantly associated with better OS (Table II). OS was 89%, 90%, and 79% at 1 year, and 85%, 61%, and 62% at 3 years in patients who underwent autologous HSCT in CR, partial remission (PR), and the disease status other than CR/PR, respectively (Fig. 1B).

PFS, RR, and NRM at 1 year and 3 years were 68%, 25%, and 6%, and 59%, 32%, and 8%, respectively (Fig. 1C,D). Through the univariate and multivariate analyses, female, disease status of CR, and better PS at HSCT were significantly associated with better PFS (Table III).

Seven of 298 patients (2%) who underwent their first autologous HSCT developed a secondary malignancy. Two patients had a secondary solid tumor (colon cancer and brain tumor at 214 days and 1695 days from HSCT, respectively), and a patient who developed colon cancer died of it. Five patients had a secondary hematological malignancy (myelodysplastic syndrome at 78, 88, and 287 days from HSCT, and diffuse large B-cell lymphoma at 249 and 755 days from HSCT, respectively). None of them died directly of their secondary hematological malignancies.

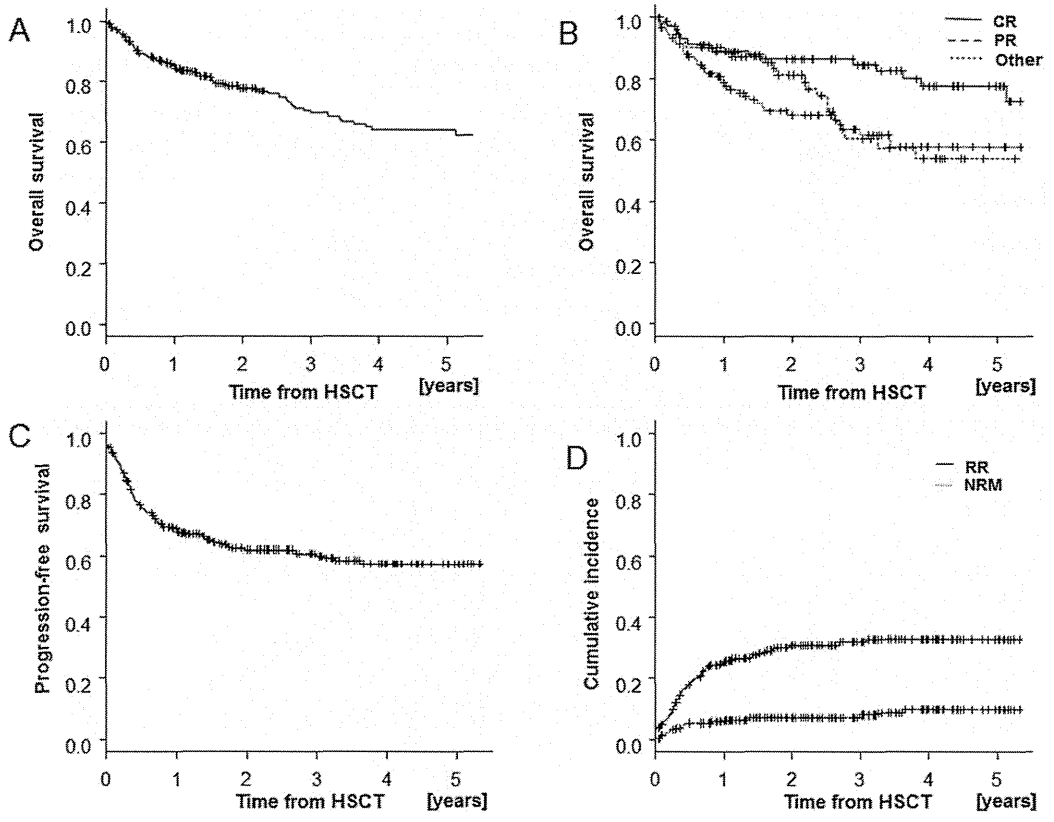

Figure 1. Overall survival from transplantation in all patients who underwent autologous HSCT (A) and in patients who underwent autologous HSCT in various disease statuses (B). Progression-free survival (C), relapse/progression rate (RR), and non-relapse/progression mortality (NRM) (D) in patients who underwent autologous HSCT.

TABLE II. Prognostic Factors for Overall Survival in Patients Who Underwent Their First Autologous HSCT

		Univariate analysis		Multivariate analysis	
		Relative Risk (95% C.I.)	*P* value	Relative Risk (95% C.I.)	*P* value
Sex	**Male**	1	0.074	1	0.049
	Female	0.62 (0.37–1.05)		0.58 (0.34–1.00)	
Clinical stage at diagnosis	**1,2**	1	0.031		
	3,4	1.66 (1.05–2.64)			
B symptoms at diagnosis	**–**	1	0.088		
	+	1.47 (0.94–2.28)			
Age at HSCT	**<40**	1	0.042	1	0.011
	≥40	1.57 (1.02–2.43)		1.72 (1.09–2.72)	
Disease status at HSCT	**CR**	1		1	0.006
	PR	2.01 (1.08–3.73)	0.014	2.28 (1.20–4.33)	
	Other status	2.27 (1.30–3.96)		2.50 (1.40–4.46)	
PS at HSCT	**0,1**	1		1	
	2–4	9.94 (5.32–18.56)	<0.001	9.89 (5.19–18.83)	<0.001

C.I., confidence interval; HSCT, hematopoietic stem cell transplantation; CR, complete remission; PR, partial remission; PS, performance status.

Outcome of a first allogeneic HSCT

With a median follow-up time from HSCT of 948 days (range: 104–3214 days) for survivors, OS from HSCT in the 122 patients who underwent their first allogeneic HSCT was 61% at 1 year and 43% at 3 years (Fig. 2A). If we consider only the 75 patients who underwent allogeneic HSCT after relapse following autologous HSCT, OS was 66% at 1 year and 42% at 3 years (Fig. 2B). Through the univariate and multivariate analyses, sex and PS at HSCT were significantly associated with better OS (Table IV). The history of previous autologous HSCT [relative risk (RR), 95% confidence interval (C.I.): 1.017 (0.62–1.66), $P = 0.95$] and conditioning intensity [RR (95% C.I.): 0.72 (0.43–1.20), $P = 0.20$] did not affect OS.

PFS, RR, and NRM at 1 year and 3 years were 45%, 27%, and 29%, and 31%, 37%, and 32%, respectively (Fig. 2C,D). Through the univariate and multivariate analyses, female and better PS at HSCT were significantly associated with better PFS (Table V). We evaluated the influence of graft-versus-host disease (GVHD). In 87 patients who were surviving without relapse/progression at least 60 days after HSCT, 62 and 46 patients experienced acute GVHD in any grade and Grade II–IV acute GVHD, respectively. In 66 patients who were surviving without relapse/progression at least 150 days after HSCT, 31 patients experienced chronic GVHD. The presence of acute GVHD in any grade, Grade II–IV acute GVHD, and chronic GVHD did not influence PFS ($P = 0.710$, $P = 0.460$, and $P = 0.834$, respectively),

TABLE III. Prognostic Factors for Progression-Free Survival in Patients Who Underwent Their First Autologous HSCT

		Univariate analysis		Multivariate analysis	
		Relative Risk (95% C.I.)	*P* value	Relative Risk (95% C.I.)	*P* value
Sex	**Male**	1	0.090	1	0.023
	Female	0.68 (0.44–1.06)		0.61 (0.39–0.96)	
Clinical stage at diagnosis	**1,2**	1	0.071		
	3,4	1.44 (0.97–2.15)			
B symptoms at diagnosis	**–**	1	0.055		
	+	1.46 (0.99–2.15)			
Disease status at HSCT	**CR**	1	0.013	1	0.004
	PR	2.04 (1.22–3.42)		2.10 (1.24–3.57)	
	Other status	1.82 (1.14–2.91)		1.96 (1.21–3.20)	
PS at HSCT	**0,1**	1	<0.001	1	<0.001
	2–4	5.14 (2.79–9.47)		4.72 (2.53–8.81)	

C.I., confidence interval; HSCT, hematopoietic stem cell transplantation; CR, complete remission; PR, partial remission; PS, performance status

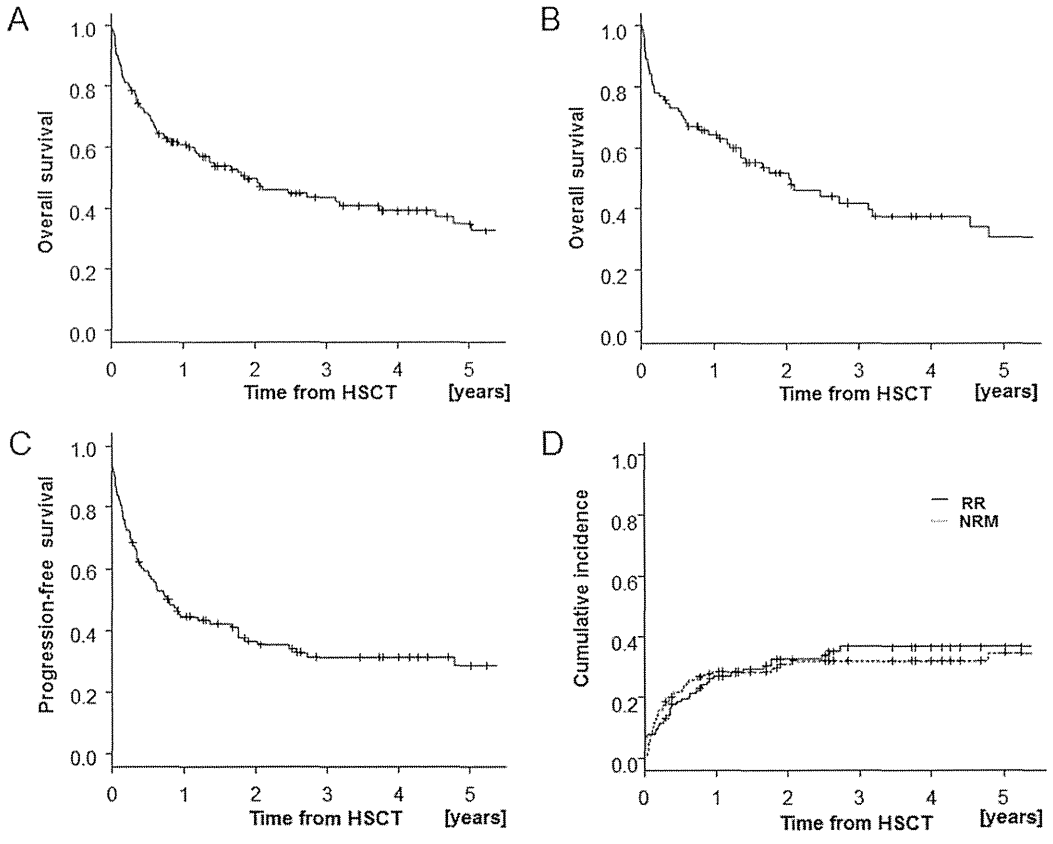

Figure 2. Overall survival from transplantation in all patients who underwent allogeneic HSCT (A) and in patients who underwent allogeneic HSCT after relapse following autologous HSCT (B). Progression-free survival (C), relapse/progression rate (RR), and non-relapse/progression mortality (NRM) (D) in patients who underwent allogeneic HSCT.

RR ($P = 0.136$, $P = 0.170$, and $P = 0.551$, respectively), and NRM ($P = 0.319$, $P = 0.068$, and $P = 0.588$, respectively).

Only one patient had a secondary malignancy (solid tumor; detailed information was not obtained).

Outcome of a first allogeneic HSCT without a previous autologous HSCT

A first allogeneic HSCT without a previous autologous HSCT was performed in 40 patients. OS from HSCT in these patients was 53% at 1 year and 45% at 3 years, and was significantly inferior to that in patients who underwent their first autologous HSCT (Fig. 3). Through the univariate (Table VI) and multivariate analyses, patients who underwent allogeneic HSCT as a first HSCT were more likely to have B symptoms at diagnosis and undergo HSCT in the worse disease status. The performance of allogeneic HSCT as a first HSCT was significantly associated with worse OS, even after the correction by the presence of B symptoms at diagnosis and disease status at HSCT.

Discussion

Many studies have reported the efficacy of autologous HSCT for relapsed and/or refractory HL. In our study, 3y OS was 70% in all patients who underwent autologous HSCT (Fig. 1A), and was

TABLE IV. Prognostic Factors for Overall Survival in Patients Who Underwent Their First Allogeneic HSCT

		Univariate analysis		Multivariate analysis	
		Relative risk (95% C.I.)	*P* value	Relative risk (95% C.I.)	*P* value
Sex	**Male**	1	0.011	1	0.018
	Female	0.49 (0.28–0.85)		0.49 (0.28–0.89)	
Disease status at HSCT	**CR**	1	0.066		
	PR	1.20 (0.46–3.11)			
	Other status	2.01 (1.05–3.86)			
PS at HSCT	**0,1**	1	<0.001	1	<0.001
	2–4	3.84 (2.12–6.96)		3.58 (1.94–6.61)	
Donor relationship	**MR**	1	<0.001		
	MMR	0.97 (0.48–1.96)			
	MUR	1.11 (0.53–2.31)			
	MMUR	3.31 (1.66–6.60)			
	CB	4.42 (2.07–9.42)			
Conditioning regimen including TBI	–	1	0.033		
	+	1.68 (1.04–2.71)			

C.I., confidence interval; HSCT, hematopoietic stem cell transplantation; CR, complete remission; PR, partial remission; PS, performance status; MR, human leukocyte antigen (HLA)-matched related; MMR, HLA-mismatched related; MUR, HLA-matched unrelated; MMUR, HLA-mismatched unrelated; CB, cord blood; TBI, total body irradiation.

TABLE V. Prognostic Factors for Progression-Free Survival in Patients Who Underwent Their First Allogeneic HSCT

		Univariate analysis		Multivariate analysis	
		Relative risk (95% C.I.)	*P* value	Relative risk (95% C.I.)	*P* value
Sex	**Male**	1	0.028	1	0.045
	Female	0.55 (0.32–0.94)		0.56 (0.32–0.99)	
Disease status at HSCT	**CR**	1	0.054		
	PR	1.83 (0.74–4.53)			
	Other status	2.29 (1.16–4.51)			
PS at HSCT	**0,1**	1		1	<0.001
	2–4	3.00 (1.64–5.49)	<0.001	2.83 (1.55–5.19)	
Donor relationship	**MR**	1	0.005		
	MMR	0.77 (0.37–1.59)			
	MUR	0.89 (0.45–1.77)			
	MMUR	2.10 (1.10–3.99)			
	CB	3.10 (1.43–6.69)			

C.I., confidence interval; HSCT, hematopoietic stem cell transplantation; CR, complete remission; PR, partial remission; PS, performance status; MR, human leukocyte antigen (HLA)-matched related; MMR, HLA-mismatched related; MUR, HLA-matched unrelated; MMUR, HLA-mismatched unrelated; CB, cord blood.

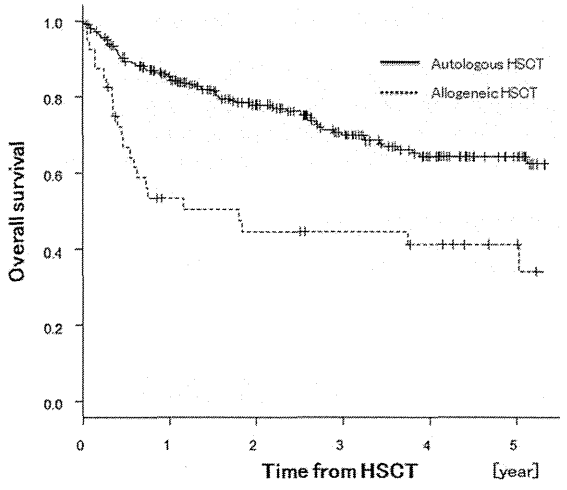

Figure 3. Among patients who had not received HSCT previously, overall survival in those who underwent allogeneic HSCT was significantly inferior to that in those who underwent autologous HSCT.

comparable to that in previous studies [4,12,13]. In addition, OS was favorable even in patients who underwent autologous HSCT in the disease status other than CR, although the disease status was associated with OS, which was similar to the results in many other studies [4,12,13]. We have to consider that clinical response was evaluated without positron-emission tomography (PET) in most of our patients. Part of patients who were evaluated as non-remission based on computed tomography (CT) might have undergone autologous HSCT in CR with PET-based assessment. The difference between OS and PFS might be attributed to the effectiveness of salvage therapy including allogeneic HSCT, which was difficult to evaluate precisely because information as to the performance of allogeneic HSCT after relapse/progression was lacking in a part of patients.

Allogeneic HSCT should be effective in prolonging OS even for relapsed HL after autologous HSCT, compared to conventional therapy [14]. In our study, 3y OS was 43% in all patients who underwent allogeneic HSCT, including those who had a previous autologous HSCT (Fig. 2A). Recently, many studies have mainly used reduced-intensity conditioning for allogeneic HSCT, and most of these patients had previously undergone autologous HSCT [15–17]. Sureda *et al.* compared the outcomes of allogeneic HSCT for patients with relapsed and refractory HL with myeloablative conditioning to those with reduced-intensity conditioning [18]. They reported that a lower NRM and a better OS were observed in patients who had been treated with reduced-intensity conditioning. In our study, the conditioning intensity did not influence OS. However, if we considered only patients who previously had undergone autologous HSCT,

TABLE VI. Characteristics of Patients Who Underwent HSCT Without Previous HSCT

		Autologous HSCT (n =298)	Allogeneic HSCT (n = 40)	P value
Patient characteristics at diagnosis				
Sex	Male	200 (57%)	24 (60%)	0.378
	Female	98 (43%)	16 (40%)	
Clinical stage at diagnosis	1,2	130 (44%)	13 (33%)	0.232
	3,4	166 (56%)	26 (65%)	
B symptoms at diagnosis	−	176 (59%)	13 (33%)	0.003
	+	116 (39%)	25 (63%)	
Patient characteristics at HSCT				
Age at HSCT	<40	170 (57%)	27 (68%)	0.235
	≥40	128 (43%)	13 (32%)	
Disease status at HSCT	CR	103 (35%)	4 (10%)	<0.001
	PR	76 (25%)	8 (20%)	
	Other status	119 (40%)	28 (70%)	
PS at HSCT	0,1	277 (93%)	29 (73%)	0.004
	2-4	18 (6%)	8 (20%)	

CR, complete remission; PR, partial remission; PS, performance status.

patients who were treated with reduced-intensity conditioning tended to have a better OS (P = 0.08). In patients who underwent allogeneic HSCT, PS at HSCT, instead of the disease status at HSCT, was significantly associated with OS in this study. The fact that the disease status was significantly associated with PS at allogeneic HSCT (P = 0.038, Fisher's exact test) might offset the influence of the disease status at HSCT on OS. Similarly, donor relationship was the significant factor for OS in a univariate analysis, but not in a multivariate analysis. Some clinical factors, other than the donor availability, might influence the donor selection, and weaken the association between donor relationship and OS. However, we could not detect such factors. In our study, sex was significantly associated with OS even through a multivariate analysis. It was demonstrated that the disadvantage of male sex, which was a known adverse prognostic factor in HL at diagnosis [19], persisted even after the performance of allogeneic HSCT.

Some studies have suggested the existence of a graft-versus-Hodgkin lymphoma effect [18,20,21]. In our study, the presence of acute or chronic GVHD did not affect PFS and RR. Acute or chronic GVHD were not associated with PFS and RR even if we analyzed only patients who underwent allogeneic HSCT in the disease status other than CR or patients who underwent allogeneic HSCT with reduced-intensity conditioning (data not shown). A graft-versus-Hodgkin lymphoma might have a very limited effect in our patients who underwent allogeneic HSCT for very advanced HL. We did not have enough patients to evaluate the role of donor lymphocyte infusion.

Recently, brentuximab vedotin has been shown to offer promising results, without severe adverse effects, even in patients with relapsed HL after autologous HSCT [22]. It has also been reported that the administration of brentuximab vedotin might be safe and effective both before and after allogeneic HSCT [23,24]. Considering that a graft-versus-Hodgkin lymphoma effect might have only a limited effect, the combination of allogeneic HSCT and brentuximab vedotin following HSCT deserve evaluation as new treatment strategy to prevent relapse after allogeneic HSCT.

The role of allogeneic HSCT as a first HSCT remains to be determined. Akpek *et al.* compared autologous HSCT and allogeneic HSCT from an HLA-matched sibling for patients with relapsed and refractory HL who had not received HSCT previously [20]. They demonstrated that there were no significant differences in OS and RR. On the other hand, OS in patients who underwent allogeneic HSCT was significantly inferior to that in patients who underwent autologous HSCT in our study. This might be attributed to a difference in the patients' background because the selection of autologous or allogeneic HSCT was at the discretion of each institution. In fact, patients who had allogeneic HSCT as a first HSCT underwent HSCT in the worse disease status, compared to those who had autologous HSCT. Moreover, chemosensitivity or number of salvage chemotherapy before HSCT might influence the difference in OS, although we could not obtain enough data as to these factors. Allogeneic HSCT without previous autologous HSCT might be a reasonable option in selected patients with chemorefractory HL, such as young patients with good PS. Prospective studies will be needed to establish the role of allogeneic HSCT in specific situations.

In conclusion, autologous HSCT is effective in prolonging survival in patients with relapsed and refractory HL. Allogeneic HSCT might be beneficial even to relapsed HL after autologous HSCT, although establishing the role of allogeneic HSCT remains a challenge.

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特集　がん薬物療法専門医に必須の血液疾患の知識

(R-)CHOP療法が標準療法ではない悪性リンパ腫*

山口素子**

Key Words：CHOP chemotherapy, diffuse large B-cell lymphoma, rituximab, multi-drug resistance

はじめに

1970年代に米国で開発されたCHOP療法(cyclophosphamide, doxorubicin, vincristine, prednisone)[1]は，40年以上を経た現在もなおリンパ腫に対する代表的な初回化学療法レジメンに位置づけられている．その一方で，WHO分類2008年版でリンパ腫は60以上もの病型で構成される不均一な疾患群であり，CHOP療法が初回治療として適さない病型が多く存在する．

本稿では，2013年10月に刊行された「造血器腫瘍診療ガイドライン」2013年版[2]で推奨初回治療が示された代表的リンパ腫病型において，CHOP療法あるいはrituximab併用CHOP療法(R-CHOP療法)(表1)が適さないリンパ腫とその治療について解説する．

基本となる考え方

表2に，現在のわが国での日常診療で原則として(R-)CHOP療法が行われないリンパ腫と，その主な理由を列挙した．選択しない理由として，CHOP療法の抗腫瘍効果が限定的であり，ほかに有効な治療法があるとするものが最も多い．

CHOP療法は，びまん性大細胞型B細胞リンパ腫(diffuse large B-cell lymphoma；DLBCL)が主体をなす非ホジキンリンパ腫の進行期例を対象として開発された[1]．月単位に進行するDLBCLと異なり，週単位に進行するバーキットリンパ腫では，21日ごとに抗がん薬が投与されるCHOP療法での病勢コントロールは困難である．DLBCLと腫瘍細胞起源が異なるTあるいはNK細胞リンパ腫におけるCHOP療法の効果は，一般的に乏しい．DLBCLであっても，中枢神経系あるいは精巣原発のDLBCLでは，CHOP療法に含まれる抗がん薬の組織移行が不良であり，異なる治療法が必要である．

ホジキンリンパ腫では周知のように1970年代当時から放射線治療，アルキル化薬を含む化学療法を中心とした独自の治療開発が行われてきている．また，表2にはないが，リンパ形質細胞性リンパ腫/Waldenström macroglobulinemiaでは，高率にIgM血症による過粘稠症候群を伴い治療開始時に配慮が必要であること，ほかに複数の治療選択肢があることから[2]，(R-)CHOP療法が初回治療として選択されることはきわめて少ない．

以下に，表2にあげたそれぞれの(R-)CHOP療法が適さないリンパ腫とその治療について述べる．

* Standard therapy other than (R)-CHOP for lymphomas.

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表1　CHOP療法

治療薬	用量	投与方法	day 1	2	3	4	5
Cyclophosphamide	750 mg/m²	点滴静注	↓				
Doxorubicin	50 mg/m²	点滴静注	↓				
Vincristine	1.4 mg/m² (最大2 mg/body)	静注	↓				
Prednisolone	100 mg/body	内服	↓	↓	↓	↓	↓

21日間を1コースとする．R-CHOP療法：CHOP療法のday 1あるいはその前日・前々日のいずれかに，CHOP療法に先行してリツキシマブ375 mg/m²を投与する．

表2　原則として(R-)CHOP療法を行わないリンパ腫

CHOP療法非選択の理由	病型名
局所治療/病因特異的治療が有効	限局期MALTリンパ腫
CHOP療法の効果が限定的 または CHOP療法より有効な治療法が存在	中枢神経系DLBCL 精巣原発DLBCL (原発性縦隔大細胞型B細胞リンパ腫) バーキットリンパ腫 成人T細胞白血病リンパ腫 節外性NK/T細胞リンパ腫，鼻型
病型別の治療開発が進行	ホジキンリンパ腫

(R-)CHOP療法が適さないリンパ腫とその治療

1．粘膜関連リンパ組織型節外性辺縁帯リンパ腫(mucosa-associated lymphoid tissue；MALT)リンパ腫の限局例

眼窩・眼付属器と胃が代表的病変部位であり，その他，肺，皮膚などがある．一部のMALTリンパ腫では発生臓器に応じて特定の感染症あるいは炎症が病因に関与している．

このうち，胃MALTリンパ腫では*Helicobacter pylori*(HP)の病因的関与が知られ，HP陽性の限局期例ではHP除菌療法が有効であり[3]，高率(50～80%)に完全奏効が得られ，第一選択である[2]．HP陰性では放射線治療が検討されるが，HP陰性でも除菌療法に反応する例があり，日常診療では除菌を試みることも多い．t(11;18)陽性の場合は除菌不応例が多いことが知られている[4]．除菌無効例では放射線治療が検討され，放射線治療の適応とならない場合はrituximab単独療法が検討される．胃以外の節外臓器に生じたMALTリンパ腫では，限局性の場合，放射線治療，外科切除，慎重な経過観察のうちから治療が選択される．

一方，進行例では同じく低悪性度リンパ腫である濾胞性リンパ腫に準じて，R-CHOPなどのrituximab併用化学療法もしくはrituximab単独療法が考慮される．

2．一部の節外原発DLBCL

CHOP療法に含まれる治療薬のうち，vincristineとdoxorubicinは脳血液関門を通過しない．このため，中枢神経系原発DLBCLに対するR-CHOP療法の効果は限定的であり，大量methotrexate(3.5 g/m²以上)を基本とした化学療法が選択される．引き続いて全脳照射を行うことで治療効果の持続が期待されるものの，しばしば重篤な神経毒性が経験され，追加照射の縮小化を目指した治療開発が進行中である．2013年に米国から報告されたR-MPV療法(rituximab, methotrexate, procarbazine, vincristine)の場合，5コース後に完全奏効，もしくは部分奏効で2コース追加後に完全奏効が得られた場合は引き続く全脳照射の線量を23.4 Gyに減じ，それ以外では45 Gyとするものであり[5]，良好な治療効果が日常診療で確認されつつある．

精巣原発DLBCLでは初回治療としてR-CHOP療法が選択されるものの，単独では中枢神経系再発率が通常のDLBCLの場合(5%未満)と比較し

て高いことが知られている(診断後10年間で15%)[6]．予防的な抗がん薬髄腔内投与，および化学療法終了後に健側を含む放射線治療の追加が第II相試験の結果から推奨されている[7]．

DLBCLの特殊病型で縦隔巨大腫瘤を特徴とする原発性縦隔大細胞型B細胞リンパ腫では，R-CHOP療法など化学療法を行ったのち，経験的に放射線治療が追加されてきた．2013年に米国から，5cm以上の縦隔腫瘤を有する初発患者に対して，多剤耐性(multi-drug resistance；MDR)克服を目指した抗がん薬の持続点滴を特徴とするdose-adjusted (DA)-EPOCH-R療法(etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab)6～8コース単独の第II相試験の結果が報じられ，観察期間中央値63か月での登録51例における5年無イベント生存割合が93%と良好であった[8]．現在，日常診療で急速に治療の見直しがされつつあるDLBCL病型である．

3．Burkittリンパ腫

高悪性度リンパ腫の代表的病型であり，週単位の病勢進行，高LDH血症，高尿酸血症が特徴的である．治療はもともと小児例に対して開発された強力な多剤併用化学療法が選択される．代表的なレジメンにCODOX-M/IVAC療法[9]があり，わが国では国内適応承認量および安全性の理由からmethotrexateなどの投与量を減じたmodified CODOX-M/IVAC療法[10]が好んで選択されている．2013年にDA-EPOCH-R療法の優れた有効性(観察期間中央値86か月時点で全生存割合100%)が，13例と少数での解析ではあるが報じられ[11]，CODOX-M/IVAC療法が適応とならない高齢者あるいは臓器機能低下例で今後期待される治療である．

Burkittリンパ腫では化学療法への反応がきわめて良好である反面，治療早期に発生する腫瘍崩壊症候群に注意が必要である．

4．成人T細胞白血病・リンパ腫(adult T-cell leukemia-lymphoma；ATL)

ATLのうちaggressive ATL〔ATLの臨床病型分類[12]のうち急性型，リンパ腫型，および予後不良因子(LDH，アルブミン，BUNのいずれか1つ以上が異常値)を有する慢性型〕[2]の予後はきわめて不良である．ATL腫瘍細胞にはMDRに関与するP糖タンパクが診断時でも高率に発現が認められること，再発例の過半数で化学療法後の新病変が中枢神経系に認められたことから[13]，MDR非関連薬を含めた多剤併用化学療法に抗がん薬髄腔内投与による中枢神経系予防を組み入れたVCAP-AMP-VECP療法(mLSG15療法)が開発された．国内でのランダム化第III相試験で2週間隔CHOP療法より有効と判断され[14]，aggressive ATLの初回推奨治療と位置づけされている[2]．治療反応性が認められ，臓器機能が保たれ，HLA一致血縁・非血縁ドナーが得られた場合は同種造血幹細胞移植が検討される．Indolent ATL(くすぶり型，予後不良因子を有さない慢性型)[2]では化学療法による生存期間の延長が得られず，aggressive ATLへ進展するまで無治療経過観察することが推奨されている．ATL患者の90%以上で腫瘍細胞に発現するCCR4の抗体薬であるmogamulizumab[15]が再発・難治例を端緒として導入されつつある．

5．節外性NK/T細胞リンパ腫，鼻型

鼻腔およびその周辺組織に好発し，著明な壊死，Epstein-Barr virus関連などを特徴とする節外主体のリンパ腫である．東アジアなどわが国で頻度が高く，65%以上が限局性である．本病型でもP糖タンパクが腫瘍細胞に発現していることが知られており，MDR関連薬(vincristine, doxorubicinなど)を主体とするCHOP療法の治療効果は不良である．この約10年間に行われた臨床試験の成果により予後が劇的に改善し，現在NK/T細胞リンパ腫はCHOP療法が適さないリンパ腫の代表といえる．

鼻腔ないしその周辺臓器原発で病変が頸部リンパ節までにとどまっている場合(IE, IIE期)，病変部放射線治療と減量DeVIC療法(dexamethasone, etoposide, ifosfamide, carboplatin)とを同時に開始するRT-2/3DeVIC療法[16]が最も推奨される．わが国での第I/II相試験における5年生存割合は70%であった．一方，鼻腔(周辺)原発で病変が頸部リンパ節を超えて拡がっている場合，あるいは皮膚など鼻腔(周辺)以外での発生例では，L-asparaginaseを主とする化学療法であるSMILE療法(steroid＝dexamethasone, methotrexate, ifosfamide, L-asparaginase, etoposide)[17]が初回

治療で推奨されている．

6．ホジキンリンパ腫

病理組織標本で特徴的巨細胞の出現を認める欧米諸国に多いリンパ腫である．連続性の進展様式，放射線治療への良好な反応性から，独自の治療開発が行われている．わが国ではホジキンリンパ腫を早期ホジキンリンパ腫と進行期ホジキンリンパ腫の2群に分け，前者ではABVD療法(doxorubicin, bleomycin, vinblastine, dacarbazine)4コース後病変部放射線治療[18]，後者ではABVD療法単独[19]を推奨治療としている[2]．早期ホジキンリンパ腫のうちリスク因子を有さない早期予後良好群では，ABVDのコース数を4から2に減らし，病変部放射線治療の総線量を30 Gyから20 Gyに減じても有効性に差がないと報じられたが[20]，国内での治療実績はまだ乏しい．

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