diseases after chemotherapy. After year 1996, patients aged 65 or younger with age adjusted IPI score (scored by stage ≥3, elevated LDH, number of extranodal involvement ≥2) of two or three were generally offered an option of upfront autologous stem cell transplantation (ASCT) if patients achieve CR or partial response (PR) after induction therapy, and seven such patients underwent ASCT as a part of primary treatment. Patients experiencing refractory or relapsed disease after initial treatment were treated with salvage chemotherapy containing high-dose cytarabine and etoposide [20, 21], and four patients underwent ASCT as consolidative therapy in the salvage settings. Actual initial treatments are summarized in Table 1.

3.2 Pretreatment SUVmax and its association with other characteristics

The median SUVmax was 18.1 (range 2.0–36.4). All, but five patients showed abnormal PET scans detecting the predominant lesions with abnormal FDG uptake. Five patients without apparent abnormality on PET all had stage I gastric DLBCL which were not detectable by CT scans either. In these patients, lymphoma was confirmed only by upper endoscopy with biopsy [22]. PS ≥ 2 were associated with high SUVmax ($p = 0.01$). Ki-67 percentage was available in 24 patients, in whom weak, but positive association between Ki-67 and SUVmax was observed ($r = 0.41$). It should be noted, however, that the biopsy was generally performed at easily accessible lesion, which was not necessarily the predominant lesion where SUVmax was calculated. There were no significant association between high SUV and other characteristics, such as stage, LDH, IPI, bulky disease or immunophenotype.

To determine the optimal cut-off value of SUVmax to divide patients into two prognostic groups, we assessed CR rate, OS and PFS using cut-off values of 15, 20, 25 and 30. The numbers of patients grouped in "high SUVmax" were 74, 49, 32 and 16 for each cut-off values, respectively. CR rate was significantly low in patients with SUVmax ≥ 30 than in those with SUVmax < 30 as detailed later. Likewise, PFS curves did not separate well when cut-off value was 25 or less, but did moderately separate at 30 (Fig. 1). OS curves separated best when the cut-off value was 20 or larger (Fig. 2 for cut-off value 30). Thus, we determined the cut-off value for "high SUVmax" at 30 in this study.

3.3 Factors associated with CR rate

In this study, 96 patients were evaluable for treatment response after R-CHOP, based on revised IWG criteria [23]. In responding patients, response was primarily evaluated by post-R-CHOP PET scan about 2 months after the completion of all initially planned therapy. In patients with gastric

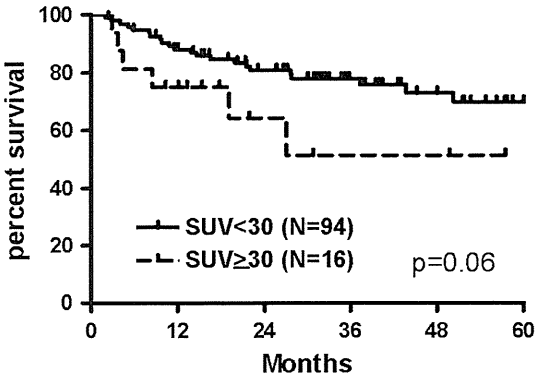

Fig. 1 Progression free survival according to SUVmax using cut off value of 30

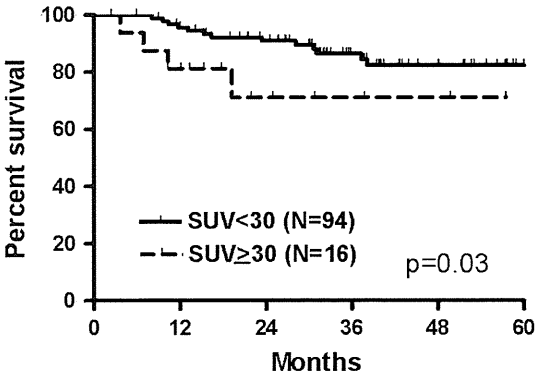

Fig. 2 Overall survival according to SUVmax using cut off value of 30

DLBCL (in whom 5 showed no abnormality in pretreatment PET scan), complete response was confirmed with PET scan as well as gastrointestinal endoscopy and biopsy.

CR rate of all patients was 72%. CR rates of patients with SUV < 30, and those with SUV ≥ 30 were 79 and 44%, respectively ($p < 0.01$). In addition, it should be noted that up to 31% of patients with SUV ≥ 30 experienced progressive disease within 6 months after starting initial treatment. Univariate analysis using logistic regression model revealed that PS ≥ 2, serum soluble interleukin-2 receptor (sIL2-R) ≥ 1,000 U/ml, presence of bulky disease, SUV ≥ 20, SUV ≥ 25 and SUV ≥ 30 were significantly associated with lower CR rate. IPI risk group was not associated with CR rate in this study. Multivariate analysis revealed that bulky disease (odds ratio 3.61 [1.32–9.89], $p = 0.013$) and SUV ≥ 30 (odds ratio 3.93 [1.22–12.7], $p = 0.022$) were significantly associated with lower CR rate.

3.4 Progression-free survival

The median follow-up duration of survival patients was 35.4 months. The estimated 3-year PFS rate of all patients

was 75%. The 3-year PFS rates in patients with SUV < 30 and those with SUV ≥ 30 were 78 and 47%, respectively ($p = 0.06$, Fig. 1). Univariate analysis revealed that PS ≥ 2, higher IPI risk group, sIL2-R ≥ 1,000 U/ml, presence of bulky disease, bcl-2 expression, MUM-1 expression and SUV ≥ 30, were significantly associated with shorter PFS duration.

By multivariate analysis, higher IPI risk group (hazard ratio (HR) 2.59 [1.21–5.55], $p = 0.014$), presence of bulky disease (HR 4.28 [2.00–9.14], $p < 0.001$) and SUV ≥ 30 (HR 2.69 [1.06–6.77], $p = 0.036$) were independently associated with shorter PFS duration (Table 2). We next performed a separate analysis according to IPI risk group. SUV ≥ 30 was significantly associated with shorter PFS independent of bulky disease in patients with IPI high risk (HR 6.74 [1.35–33.6], $p = 0.020$), but not in patients with IPI low risk (HR 1.96 [0.55–6.97], $p = 0.300$, Table 3).

3.5 Overall survival

The estimated 3-year OS rate in all patients was 84%. The 3-year OS rates in patients with SUV < 30 and those with SUV ≥ 30 were 86 and 71%, respectively ($p = 0.03$, Fig. 2). Univariate analysis revealed that PS ≥ 2, higher IPI risk group, low albumin, sIL2-R ≥ 1,000 U/mL, presence of bulky disease, bcl-2 expression SUV ≥ 20, SUV ≥ 25 and SUV ≥ 30 were significantly associated with shorter OS duration.

Multivariate analysis for OS revealed that higher IPI risk group (HR 3.50 [1.35–9.07], $p = 0.010$), presence of bulky disease (HR 3.82 [1.48–9.85], $p = 0.005$) and SUV ≥ 30 (HR 3.21 [1.01–10.2], $p = 0.048$) were independently associated with shorter OS duration (Table 2). In the analysis excluding patients who received up-front ASCT, prognostic significance of SUV was marginal (potentially due to the smaller number of patients analyzed, HR 2.63, 95%CI 0.95–7.44). We next performed a separate analysis based on the IPI risk group. SUV ≥ 30 was associated with shorter OS independent of bulky disease in patients with IPI high risk (HR 6.45 [0.98–42.5], $p = 0.052$), but not in patients with IPI low risk (HR 2.65 [0.53–13.2], $p = 0.235$, Table 3). When we analyzed SUVmax as a linear variable, SUVmax was still a significant risk factor (HR 1.04 [1.00–1.09], $p = 0.047$) independent from IPI risk group (HR 2.68 [1.13–6.34], $p = 0.025$) and Bulky disease (HR 2.93 [1.24–6.94], $p = 0.014$).

Table 2 The result of multivariate analyses for progression-free survival and overall survival

All patients	Hazard ratio (95% CI) for PFS	*p*
Progression-free survival		
IPI H/H-I	2.59 (1.21–5.55)	0.014
Bulky disease	4.28 (2.00–9.14)	<0.001
SUVmax ≥ 30	2.69 (1.06–6.77)	0.036
Overall survival		
IPI H/H-I	3.50 (1.35–9.07)	0.010
Bulky disease	3.82 (1.48–9.85)	0.005
SUVmax ≥30	3.21 (1.01–10.2)	0.048

PFS progression-free survival, *OS* overall survival, *IPI* International Prognostic Index, *H* high, *H-I* high intermediate, *SUV* standard uptake value

4 Discussion

Identification of poor prognostic group is essential to optimize treatment approaches in patients with DLBCL. In the present study, we showed that high SUVmax was associated with shorter OS and shorter PFS, independent from IPI. High SUV was also associated with lower CR rate. It is, particularly, notable in patients with SUV ≥ 30 that CR rate was 44%, and progressive disease rate was as high as 31%. When we analyzed SUVmax as a linear variable, it was also associated with shorter survival independent of other factors and such trend was observed both in IPI lower risk group and in higher risk group when analyzed separately.

PET scan is a valuable tool in the assessment of patients with malignant diseases. However, there remain major issues in interpretation of the SUVmax. Actual protocols for PET scan often vary significantly by centers, and the

Table 3 The result of multivariate analyses for progression free survival and overall survival separated with IPI risk

All patients	HR (95% CI) for PFS	*p*	HR (95% CI) for OS	*p*
IPI L/L-I				
Bulky disease	2.44 (0.88–6.75)	0.085	2.51 (0.62–10.1)	0.195
SUVmax ≥ 30	1.96 (0.55–6.97)	0.300	2.65 (0.53–13.2)	0.235
IPI H/H–I				
Bulky disease	10.0 (3.01–33.4)	<0.001	6.01 (1.58–23.3)	0.009
SUVmax ≥ 30	6.74 (1.35–33.6)	0.020	6.45 (0.98–42.5)	0.052

HR hazard ratio, *PFS* progression-free survival, *OS* overall survival, *IPI* International Prognostic Index, *L* low, *L-I* low intermediate, *H* high, *H-I* high intermediate, *SUV* standard uptake value

quantification of SUV is easily affected by the time after FDG infusion and by blood glucose level. In fact in our study, blood glucose levels were not measured before PET scan, which is one of the limitations of this study. The value of SUV in oncology has been extensively discussed in the literature, and SUV has even been called "silly useless value" by those against the use of SUV [24]. Furthermore, studies have shown only moderate reproducibility of interpretation of PET scan among nuclear medicine experts [25]. We set the cut-off value for SUVmax at 30 which best separated patients into two prognostic groups, but this threshold may differ in different PET scan protocol. Standardization of the protocol is essential to further validate the result of our study.

In conclusion, we showed potential prognostic value of high SUV independent of IPI in patients with DLBCL. Standardization of the acquisition and processing protocols are urgently needed and larger scale prospective studies are necessary to validate our findings.

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Conflict of interest None.

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ORIGINAL ARTICLE

Allogeneic hematopoietic stem cell transplantation for ATL with central nervous system involvement: The Nagasaki Transplant Group experience

Takuya Fukushima · Jun Taguchi · Yukiyoshi Moriuchi · Shinichiro Yoshida · Hidehiro Itonaga · Koji Ando · Yasushi Sawayama · Yoshitaka Imaizumi · Daisuke Imanishi · Tomoko Hata · Yasushi Miyazaki

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Abstract Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is regarded as a curative option for aggressive adult T cell leukemia-lymphoma (ATL). However, the efficacy and safety of allo-HSCT for ATL with central nervous system (CNS) involvement, which is highly resistant to chemotherapy, remain controversial. We analyzed 10 ATL patients with CNS involvement who received allo-HSCT at three institutions in Nagasaki prefecture between 2000 and 2007. The 3-year overall survival rate was 40%, and the median observation time of the four surviving patients was 1532 days (range 945–2212 days). Two of four surviving patients received highly intensive local treatment for the CNS; one with 26 intrathecal injections of antineoplastic agents, and the other with whole cerebrospinal irradiation before transplantation. However, the other two patients received conventional or reduced-intensity conditioning with standard intrathecal chemotherapy. Three of the four surviving patients experienced chronic GVHD, and two of three patients with grade 3 or 4 acute GVHD were free from CNS relapse. From these data, it seems that both intensive local treatment for CNS disease and systemic GVHD contributed to the long-term control of CNS involvement. Although our data suggest that allo-HSCT is a therapeutic option for ATL with CNS disease, high transplant-related mortality (six cases) indicates the need for further studies to develop more effective procedures for CNS disease, and to reduce transplant-related morbidity.

Keywords ATL · CNS involvement · Allo-HSCT

T. Fukushima (✉) · J. Taguchi · H. Itonaga · K. Ando · Y. Imaizumi · D. Imanishi · T. Hata · Y. Miyazaki
Department of Hematology, Atomic Bomb Disease and Hibakusya Medicine Unit, Atomic Bomb Disease Institute, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan
e-mail: fukutaku@nagasaki-u.ac.jp

Y. Moriuchi · Y. Sawayama
Sasebo City General Hospital, Sasebo, Japan

S. Yoshida
National Hospital Organization Nagasaki Medical Center, Ohmura, Japan

1 Introduction

Adult T cell leukemia-lymphoma (ATL) is a peripheral T cell neoplasm caused by a specific retrovirus, human T cell lymphotropic virus type-1 (HTLV-1) [1–4], and has different features from other non-Hodgkin's lymphomas (NHL). In particular, ATL is restricted to endemic areas including the west coast of Japan, and is associated with frequent hypercalcemia, predisposition to opportunistic infections, and a poor response to chemotherapy, with a median survival time (MST) of approximately 8 months [5–9].

Multicenter clinical trials for ATL conducted by the Japan Clinical Oncology Group (JCOG) have shown that standard dose chemotherapy for NHL was unable to prolong the survival time or cure any patients with the acute or lymphoma types of ATL, which is more aggressive than the chronic or smoldering types [10, 11]. So far, the chemotherapy protocol, named modified-LSG15 (mLSG15), has shown better results than biweekly CHOP, which is a dose-intensified multiagent chemotherapy regimen with a combination of 8 drugs. The progression-free survival (PFS) at 1 year in patients treated with mLSG15 was 28% and the overall survival (OS) at 3 years was 24% [12]. However, the improvement in the survival time by mLSG15 was still minimal and the efficacy of standard dose combination chemotherapy for ATL is limited.

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) was applied for these patients as an alternative option, especially for young patients in Japan [13, 14]. Recently, several reports have demonstrated that allo-HSCT using both myeloablative and reduced-intensity conditioning provides sustained long-term survival for some patients with aggressive ATL, along with the graft-versus-ATL effects [15–19]. However, transplantation-related mortality (TRM) was higher than that observed for AML, especially within 6 months after transplantation.

The central nervous system (CNS) is one of the commonly involved regions among ATL cases, not only during the progressive phase but also at the onset of ATL. Because CNS invasion of ATL is highly resistant to standard dose chemotherapy, and even to treatment with intrathecal (IT) injection of methotrexate, cytarabine and steroids, the indications for allo-HSCT for such ATL patients is controversial. In this study, to evaluate the efficacy of allo-HSCT for ATL patients with CNS involvement, we retrospectively analyzed 10 cases of allo-HSCT for these patients performed at three institutions in Nagasaki prefecture.

2 Patients and method

2.1 Patient characteristics

Between 2000 and 2007, 10 ATL patients with CNS involvement underwent allo-HSCT using both myeloablative and reduced-intensity conditioning at three institutions in Nagasaki prefecture. CNS involvement of ATL was confirmed by cytology and cell surface marker analysis using cerebrospinal fluid before transplantation. Data were collected and updated as December 2010.

The clinical characteristics of the patients are summarized in Table 1. Five patients in this study (nos. 1, 2, 3, 4, and 8) were included in the previous report of the nationwide retrospective study of the allo-HSCT for ATL by Hishizawa et al. [19] and the data of two patients (nos. 1 and 8) were updated.

The median age of patients was 48 (range 41–57 years), and the median follow-up was 441 days (range 10–2212 days). The initial subtypes of ATL were seven patients with the acute type, and three patients with the lymphoma type. Three patients had CNS involvement at onset, and the others had CNS invasion of ATL at the time of relapse or recurrence. Before the transplantation procedure, all patients received conventional chemotherapy including anthracyclines, and IT injections of cytarabine, methotrexate and prednisone with a median number of 4.5 courses (range 1–26). The median duration from diagnosis to transplantation was 134 days (range 58–481 days).

Table 1 Characteristics of ATL patients with CNS involvement undergoing allogeneic transplantation

Patient variables	
Median age (years)	48 (range 41–57)
Sex (male/female)	4/6
Subtype of ATL	
Acute	7
Lymphoma	3
Disease status at transplantation	
CR	1
PR	2
NC	2
Relapse	1
PIF	4
Donor	
HLA-matched related	7
CB	3
Source of stem cells	
BM	3
PB	4
CB	3
Conditioning	
TBI/CY	4
TBI/CY/CA	1
BU/CY	1
Flu/Mel	3
Flu/BU	1
GVHD prophylaxis	
CsA + MTX	7
CsA	1
TCR + MTX	1
TCR	1

CR complete remission, *PR* partial remission, *NC* no change, *PIF* primary induction failure, *CB* cord blood, *BM* bone marrow, *PB* peripheral blood, *TBI* total body irradiation, *CY* cyclophosphamide, *CA* cytarabine, *BU* busulfan, *Flu* fludarabine, *Mel* melphalan, *CsA* cyclosporin, *MTX* methotrexate, *TCR* tacrolimus

2.2 Transplantation

The source of stem cells was bone marrow (BM) from an HLA-matched sibling in three, peripheral blood stem cells (PBSCs) from an HLA-matched sibling in three and 2 loci HLA-mismatched in one, and cord blood (CB) in three. All patients were transplanted with a sufficient number of mononuclear cells (over 3×10^8 per kg in BM, and 2×10^7 per kg in CB) or CD34-positive cells (over 2×10^6 per kg in PBSCs).

Since transplantation was performed following the protocol of each institution, the conditioning regimen, prophylaxis for graft-versus-host disease (GVHD) and treatment for CNS regions varied among institutions. Six patients received myeloablative conditioning: five received total body irradiation (TBI) (total 12 Gy, 6 fractions) and cyclophosphamide (CY) (60 mg/kg i.v. daily for 2 days)

with or without whole cerebrospinal irradiation (WCSI, total 10 Gy), and one patient received busulfan (4 mg/kg p.o. daily for 4 days) and CY with 10 Gy WBSI. Four patients received reduced-intensity conditioning: two fludarabine (Flu, 25 mg/m^2 i.v. daily for 5 days) and melphalan (Mel, 80 mg/m^2 i.v. daily for 1 day) with or without 2 Gy TBI, and one received Flu (30 mg/m^2 i.v. daily for 6 days) and BU (4 mg/kg p.o. daily for 4 days) with 20 Gy WCSI.

2.3 Statistical analysis and definition

The OS was measured from day 0 of transplantation to death from any cause or the last known follow-up. Transplant-related mortality (TRM) was defined as death after transplantation during remission. The survival curves were estimated using the Kaplan–Meier method.

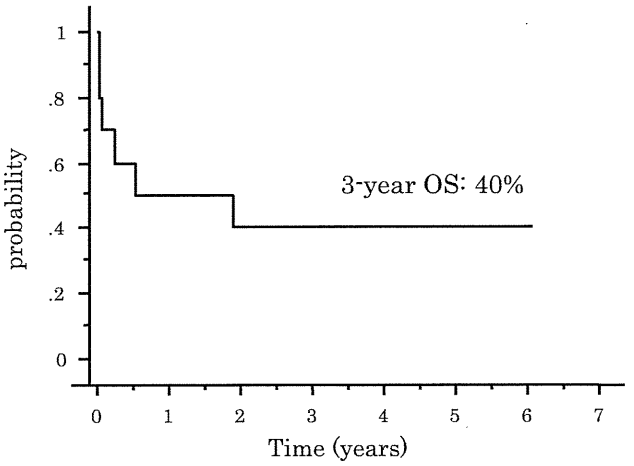

Fig. 1 OS after transplantation. The estimated 3-year OS rate was 40%

3 Results

3.1 Engraftment

Two patients were not evaluable for engraftment because of early treatment-related mortality before engraftment. Seven of eight evaluable patients achieved neutrophil regeneration, and the median number of days was 15 days (range 9–16 days). One patient did not achieve neutrophil regeneration, and died of bacterial infection on day 41.

3.2 Overall outcome

The actuarial 3-year OS was 40% after transplantation (Fig. 1). Four patients (nos. 1, 4, 9, and 10) were alive at the time of analysis (December 2010), with follow-up times from transplantation of 945, 1429, 1635, and 2212 days (Table 2). The disease status of these four patients before transplantation was refractory to conventional chemotherapy in three patients, and partial remission in one. However, after transplantation, all reached complete remission, and three of them were free from relapse of systemic and CNS diseases until the time of analysis. These four cases were transplanted from related donors, and 3 out of 4 received intensive chemotherapy and/or irradiation to the CNS separated from or as a part of conditioning regimens, such as frequent IT injections (26 times) with 12 Gy irradiation to CNS as TBI in no. 1, 12-Gy TBI in no. 9, and 20-Gy WCSI in no. 10. In the other 6 patients, 5 died within 200 days from

Table 2 Individual details of prior treatment, conditioning regimens and outcomes of the 10 ATL patients with CNS involvement

Case no.	Age/ sex	IT		WCSI (Gy)	Conditioning	Type of transplant	aGVHD	cGVHD	CNS relapse	OS (days)	Cause of death
		Before	After								
1	48/M	26	3	–	TBI/CY	PBSCT related	III	Limited	–	2212+	
2	41/M	2	21	10	TBI/CY	BMT related			+	690	PD
3	48/M	2	0	–	BU/CY	CBT unrelated			–	93	Viral infection (adenovirus)
4	57/F	1	1	–	Flu/Mel	BMT related		Extensive	+	1635+	
5	57/F	5	0	–	Flu/Mel/TBI	PBSCT related			–	15	MOF
6	52/F	5	3	10	TBI/CY	CBT unrelated	IV		+	192	PD
7	56/M	6	0	–	Flu/Mel	PBSCT related			–	41	Bacterial infection
8	47/F	5	0	–	TBI/CY/CA	CBT unrelated			–	10	MOF
9	48/F	4	1	–	TBI/CY	BMT related	IV	Extensive	–	1429+	
10	48/F	4	3	20	Flu/BU	PBSCT related			–	945+	

IT intrathecal injection, *WCSI* whole cerebrospinal irradiation, *PBSCT* peripheral blood stem cell transplantation, *BMT* bone marrow transplantation, *CBT* cord blood transplantation, *aGVHD* acute graft-versus-host disease, *cGVHD* chronic graft-versus-host disease, *OS* overall survival, *MOF* multi-organ failure

transplantation: one of progressive disease (PD) and the other four of transplantation-related toxicity. One patient (no. 2) experienced an isolated CNS relapse after allo-HSCT that was resistant to intensive IT chemotherapy and donor-leukocyte infusion. In terms of the stem cell source, three patients (nos. 3, 6, and 8) received CB transplantation (CBT) with myeloablative conditioning, but all died early after transplantation (days 10, 93, and 192).

3.3 Relapse and TRM

There were six deaths after transplantation, two due to progressive disease, and four due to TRM before day 100: two due to multi-organ failure, and one each due to adenovirus pneumonia and a bacterial infection. Three patients experienced a CNS relapse after transplantation, two patients with isolated CNS relapses and another with both CNS and systemic relapse. One of the long-term survivors experienced a CNS relapse of ATL on day 139 after transplantation (no. 4); however, a single IT injection brought about more than 1400 days of a second complete remission. The other two patients (nos. 2 and 6) died of PD. One patient (no. 2) developed an early isolated CNS relapse after transplantation, and survived over 1 year after receiving IT treatment. In this patient, a systemic relapse did not appear until the end of his clinical course.

3.4 Graft-versus-host disease

A total of three patients developed acute GVHD at a median of 24 days (range 23–25 days) of grade III–IV; however, treatment for acute GVHD such as steroids was effective. Two of the three patients who developed acute GVHD were long-term survivors. Chronic GVHD was observed in three patients, two of whom also had acute GVHD, and developed as the extensive type in two patients and the limited type in one. All four long-term survivors experienced either acute and/or chronic GVHD. Two patients who had both acute and chronic GVHD remained in complete remission for 1429 and 2212 days (nos. 1 and 9).

4 Discussion

ATL with CNS involvement is classified as the "acute" or "lymphoma" subtype, and these two are more resistant to chemotherapy than other two subtypes, "chronic" and "smoldering" [6]. Although we and others have previously reported the efficacy of allo-HSCT for ATL patients with the "acute" or "lymphoma" subtype [13–19], it remained unclear whether allo-HSCT could provide clinical effects for ATL patients with CNS involvement. Among patients with acute leukemia, it was reported that the clinical outcome after allo-HSCT was apparently worse when patients had CNS involvement compared to those without [20, 21], and a history of CNS involvement before transplantation was identified as the strongest predictive factor for CNS relapse after transplantation [22–24].

In the present study, although the total number of patients was 10, four ATL patients with CNS involvement survived more than 2.5 years after allo-HSCT. Recently, Hishizawa et al. [19] retrospectively analyzed the results of 386 cases of allo-HSCT for ATL, and reported that the OS was 33% at 3 years. Compared with the data from Hishizawa and other previously reported results, it seemed that allo-HSCT may be effective for ATL with CNS involvement.

Two out of the four long-term survivors in the present study had received intensive treatment for CNS regions: highly intensive IT chemotherapy or WCSI before transplantation, which seemed to have contributed to the local control of ATL. However, in the other two cases, there was no local treatment for CNS-ATL. In patient no. 4, who received reduced-intensity conditioning, the CNS relapse after allo-HSCT was well controlled for a long time with just one IT treatment. It is also interesting that all four survivors had either acute (grade III or IV) or extensive chronic GVHD. Although there is no clear clinical evidence that graft-versus-leukemia is effective for CNS disease after allo-HSCT [25, 26], these observations suggested the existence of possible graft-versus-ATL in the CNS, similar to the systemic graft-versus-ATL effect that has been previously reported. Recently, intrathecal infusion of donor lymphocytes by CD14 depletion of peripheral blood mononuclear cells from corresponding allogeneic donors for CNS relapse after allo-HSCT was reported to be safe [27]. It is important to develop the procedure to induce GVL effect for CNS.

Similar to our and other investigators' previous reports [15–19], the TRM was very high in this study. The fact that five patients died within 3 months from transplantation underscores the important role of supportive care after transplantation, especially for preventing and treating infections. With regard to TRM, the stem cell source also had an impact on the results. All three CBTs were unsuccessful in this study, suggesting worse results for CBT in this setting. It is true that CB would be selected as unrelated stem cell source for an urgent transplantation, such as the transplantation for cases with progressive diseases. All three cases that received CBT in this study had uncontrollable ATL when transplanted, which could be also related to the poor prognosis. However, it was also pointed out in the report by Hishizawa et al. [19] that CBT led to inferior results to related and unrelated BMT/PBSCT. Therefore, when considering CBT, extra caution is needed,

and further studies are needed to optimize the CBT procedure for ATL patients.

In conclusion, our data encourage in conducting further studies to evaluate the efficacy of allo-HSCT for ATL patients with CNS involvement, suggesting that allo-HSCT, at least from a related donor, is worth considering as a therapeutic option. It seemed that the efficacy of the procedure is probably associated with GVL effect for the CNS disease. Further studies are needed to develop transplant procedures to intensify local control and to induce the GVL effect for the CNS, as well as to reduce transplant-related morbidity and mortality.

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ORIGINAL ARTICLE

Long-term outcomes after hematopoietic SCT for adult T-cell leukemia/lymphoma: results of prospective trials

I Choi[1], R Tanosaki[2], N Uike[1], A Utsunomiya[3], M Tomonaga[4], M Harada[5], T Yamanaka[6], M Kannagi[7] and J Okamura[6], on behalf of the ATLL allo-HSCT Study Group

[1]*Department of Hematology, National Kyushu Cancer Center, Fukuoka, Japan;* [2]*Stem Cell Transplantation Unit, National Cancer Center Hospital, Tokyo, Japan;* [3]*Department of Hematology, Imamura Bun-in Hospital, Kagoshima, Japan;* [4]*Molecular Medicine Unit, Department of Hematology, Atomic Bomb Disease Institute, School of Medicine, Nagasaki University, Nagasaki, Japan;* [5]*Kyushu University Graduate School of Medical Sciences, Fukuoka, Japan;* [6]*National Kyushu Cancer Center, Institute for Clinical Research, Fukuoka, Japan and* [7]*Medical Research Division, Department of Immunotherapeutics, Tokyo Medical and Dental University, Tokyo, Japan*

We have previously conducted clinical trials of allogeneic hematopoietic SCT with reduced-intensity conditioning regimen (RIC) for adult T-cell leukemia/lymphoma (ATLL)—a disease caused by human T-lymphotropic virus type 1 (HTLV-1) infection and having a dismal prognosis. Long-term follow-up studies of these trials revealed that 10 of the 29 patients have survived for a median of 82 months (range, 54–100 months) after RIC, indicating a possible curability of the disease by RIC. However, we have also observed that the patterns of post-RIC changes in HTLV-1 proviral load over time among the 10 survivors were classified into three patterns. This is the first report to clarify the long-term outcomes after RIC for ATLL patients.
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Keywords: adult T-cell leukemia/lymphoma; allogeneic hematopoietic SCT; reduced-intensity conditioning regimen; HTLV-1 proviral load

Introduction

Adult T-cell leukemia/lymphoma (ATLL) is a peripheral T-cell malignancy that is caused by human T-lymphotropic virus type 1 (HTLV-1) infection and commonly affects individuals at an average age of 60 years. It has been reported that the 4-year survival rate was only 10.3%; in particular, patients with an acute or lymphoma subtype showed a dismal prognosis with a 4-year survival rate of approximately 5.0%.[1] Several retrospective studies for ATLL patients younger than 50 years have suggested the possible usefulness of allogeneic hematopoietic SCT (allo-HSCT) with a conventional conditioning chemotherapy regimen. However, the treatment-related mortality by conventional allo-HSCT was high (40–60%), probably due to the disease-specific immune deficiency at diagnosis.[2–4] This unacceptable level of mortality, even in the case of young patients, critically deters the applicability of conventional allo-HSCT for the general population of ATLL.

To permit the application of allo-HSCT for ATLL in patients aged more than 50 years, we can consider allo-HSCT for ATLL conditioned with reduced-intensity regimen (hereafter, allo-HSCT conditioned with reduced-intensity regimen is referred to as 'RIC'). Few retrospective studies have reported the results of RIC for ATLL so far; Shiratori *et al.*[5] followed up 15 patients after allo-HSCT (including 10 who received RIC) whose median age was 57 years and reported that the OS rate at 3 years reached 73%. Kato *et al.*[6] investigated the results of 33 patients with allo-HSCT from unrelated donors but this study included only 6 patients receiving RIC. However, our study group had previously activated the first clinical trials of RIC in 2001. These were two trials to clarify the feasibility of RIC: one studied RIC administered with immunosuppressant antithymocyte globulin (ATG) and the other studied RIC without ATG. The results have been already published elsewhere[7,8] and the treatment-related mortality in both trials collectively decreased to the 20% level, showing that RIC is a promising procedure for ATLL patients more than 50 years of age. In this report, we present the results of long-term follow-up of the two trials and discuss the longitudinal patterns of changes in HTLV-1 proviral load in survivors.

Patients and methods

The patient characteristics have been described in the previous reports.[7,8] Briefly, patients were eligible if they had ATLL of acute or lymphoma type and were aged between

Correspondence: Dr J Okamura, National Kyushu Cancer Center, Institute for Clinical Research, 3-1-1 Notame, Minami-ku, Fukuoka 811-1395, Japan.
E-mail: jyokamur@nk-cc.go.jp
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50 and 70 years. The patients were required to be in either CR or PR at the time of trial registration, and to have a HLA-identical sibling donor. The conditioning regimen consisted of fludarabine (30 mg/m^2 per day) for 5 days and BU (1 mg/kg orally per day) for 2 days. The patients in the first study also received low-dose ATG (2.5 mg/kg per day) for 2 days, whereas those in the second study did not. On day 0, G-CSF-mobilized peripheral blood grafts from their HLA-identical sibling donors were transplanted. To prevent GVHD, we continuously infused CYA (3 mg/kg per day) starting on day −1. The degree of donor–recipient chimerism in peripheral blood mononuclear cells was examined according to the previously reported method.[9] The HTLV-1 proviral load was estimated using blood samples obtained before and at 1, 2, 3, 6, 12 months and every year after transplantation. HTLV-1 proviral DNA was measured by the quantitative PCR amplification of HTLV-1 pX DNA.[10] The detection limit of the HTLV-1 proviral load was 0.5 copies per 1000 cells. The OS curve was estimated by the Kaplan–Meier method.

Results and discussion

Long-term survivors after RIC

In all, 15 and 14 patients were registered in the first and second studies, respectively. Eleven (six and five in the first and second studies, respectively) and eight (four in each study) patients died because of ATLL and the treatment, respectively. The last treatment-related death occurred 26 months after RIC. Characteristics of the remaining 10 patients (5 in each study) are summarized in Table 1. They are currently alive with a median follow-up period of 82 months after RIC (range, 54–100 months). Of the surviving patients, six and four patients had the acute and lymphoma types of ATLL. Of 10 patients, 5 received the grafts from HTLV-1-positive sibling donors. The OS rate at 60 months (5 years) was 34% (95% confidence interval, 18–51). No death was reported beyond 36 months after RIC (Figure 1).

Of the 10 survivors, 3 developed nonhematological relapse in the skin and/or lymph nodes within a half year after RIC (Table 1). However, remission was achieved again in these patients after the discontinuation of CYA, immunosuppressive agent, and the administration of additional treatments. In one of these patients, remission was achieved with the cessation of CYA alone. Two other patients were treated with systemic chemotherapy as well as local irradiation or donor lymphocyte infusion after the discontinuation of CYA, and thereafter obtained remission. These three patients survived for 100, 88 and 54 months after RIC, respectively. Because disease recurrence is usually fatal, the clinical course for the three patients was unique. It is suggested that the newly established immunological environment after RIC might have contributed to the eradication of ATLL lesions after early relapse.

All the 10 survivors developed acute GVHD (9 grades I–II and 1 grade III). Chronic GVHD was observed in all but one patient. Although immunosuppressive treatment was discontinued in 9 of the 10 patients, 1 patient is still receiving treatment due to active chronic GVHD. The development of chronic GVHD may suggest the presence of the graft-vs-ATLL effect. Of note is that 8 of 10 survivors received RIC when they were in PR after induction chemotherapy.

Kinetic patterns of HTLV-1 proviral load in long-term survivors

Serial changes in the HTLV-1 proviral load after RIC in the 10 long-term survivors are shown in Figure 2. The changes in the proviral load are heterogeneous but can be roughly classified into three patterns. In the first pattern, the proviral load became undetectable after RIC and continued to remain so; this pattern was seen in three patients. In the second pattern, the proviral load had become undetectable but returned to detectable levels thereafter; this pattern was also seen in three patients, all of whom had received RIC from HTLV-1-negative donors. Finally, in the third pattern, the proviral load had remained at the carrier level in four patients; these patients received the grafts from donors who were HTLV-1 carriers. All the 10 survivors continue to show complete donor chimera during the observation period regardless of the HTLV-1 proviral load level.

We noted that one survivor who was donated graft from an HTLV-1 carrier showed a strikingly high proviral load (nearly 1000 copies) during the first year after RIC; this

Table 1 Characteristics of long-term survivors

Age (years)	*Gender*	*ATL subtype*	*Donor status of HTLV-1*	*Status at RIC*	*Acute GVHD*	*Chronic GVHD*	*Relapse*	*Treatment after relapse*	*Current Karnofsky PS score (%)*	*Survival after RIC (months)*
62	Male	Acute	(+)	PR	I	Yes	Lynd, skin (day 28)	d/c CsA	>90	100
66	Female	Acute	(+)	PR	II	Yes	No		>90	98
51	Male	Acute	(−)	PR	II	Yes	No		>90	98
53	Male	Lymph	(−)	PR	II	Yes	No		>90	91
54	Male	Lymph	(−)	CR	II	Yes	Lynd (day 171)	d/c CsA, Rx, Cx	>90	88
55	Male	Lymph	(+)	PR	II	Yes	No		>90	75
62	Male	Acute	(+)	CR	II	Yes	No		>90	74
50	Female	Lymph	(−)	PR	I	Yes	No		>90	62
56	Male	Acute	(−)	PR	II	Yes	Skin (day 29)	d/c CsA, DLI, steroid	>90	54
53	Female	Acute	(+)	PR	III	No	No		>90	54

Abbreviations: Cx = chemotherapy; d/c = discontinued; DLI = donor lymphocyte infusion; lynd = lymph node; PS = performance status; RIC = hematopoietic stem cell transplantation conditioned with reduced-intensity regimen; Rx = radiation therapy.

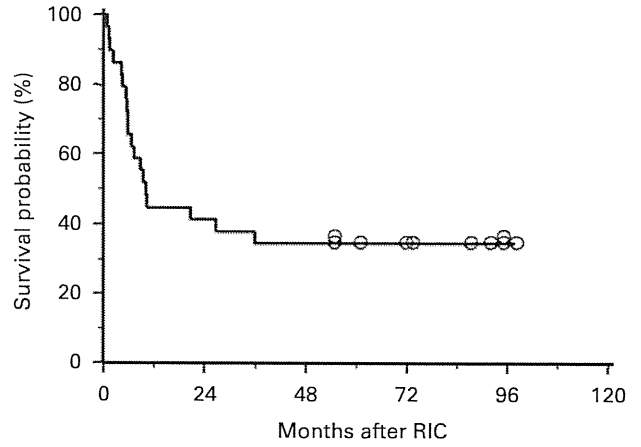

Figure 1 Kaplan–Meier curves for OS following RIC for ATLL. Circles show survivors (censored cases).

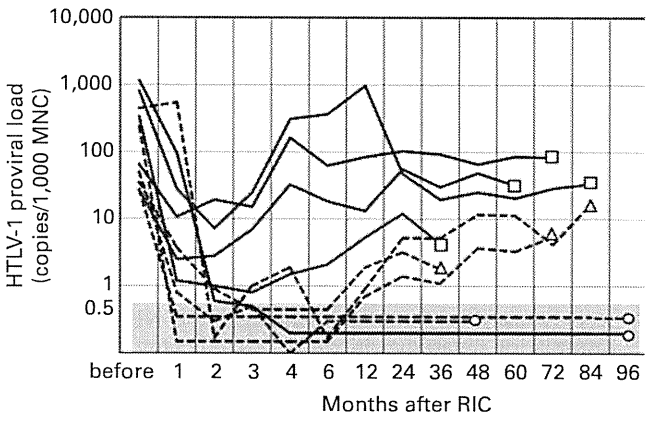

Figure 2 The longitudinal patterns of HTLV-1 proviral load after RIC in 10 long-term survivors. The HTLV-1 proviral load was measured by assaying serial blood samples after RIC by real-time PCR amplification of pX DNA and is expressed as copies per 1000 mononuclear cells (MNC). A load of less than 0.5 copies per 1000 MNC was considered undetectable, which is shown by the shaded area. A solid line indicates a patient who received a transplant from an HTLV-1 carrier donor whereas a dotted line indicates a patient from an HTLV-1-negative donor. Each circle, triangle or square indicates the latest measurement for the patient. Circle shows a pattern that the proviral load became undetectable after RIC and continued to remain so. Triangle shows a pattern that the proviral load had become undetectable but returned to detectable levels thereafter. Square shows a pattern that the proviral load had remained at the carrier level.

load then gradually decreased to the carrier level in the second year and the patient is currently surviving without any relapse. A temporary proliferation of HTLV-1-infected (nonleukemic) donor cells, as confirmed by a chimerism analysis, might have occurred due to some unknown etiology.

Conclusion

The long-term follow-up in our prospective studies has shown that one-third of the patients have survived and remain free of ATLL. We have also observed the different patterns of changes in proviral load; the pattern of changes in patients who received the grafts from HTLV-1-positive donors was different from that in patients who received the grafts from HTLV-1-negative donors. In conclusion, this is the first report on the long-term outcomes of ATLL patients who received allo-HSCT, and we have confirmed that RIC from matched sibling donors is a feasible treatment modality for ATLL, and that this treatment has a possible curative effect in patients with ATLL.

Conflict of interest

The authors declare no conflict of interest

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Rituximab monotherapy with eight weekly infusions for relapsed or refractory patients with indolent B cell non-Hodgkin lymphoma mostly pretreated with rituximab: A multicenter phase II study

Kensei Tobinai,[1,13] Tadahiko Igarashi,[2] Kuniaki Itoh,[3] Mitsutoshi Kurosawa,[4] Hirokazu Nagai,[5] Akira Hiraoka,[6,14] Tomohiro Kinoshita,[7,15] Naokuni Uike,[8] Michinori Ogura,[9,16] Shigeru Nawano,[10] Shigeo Mori,[11] Yasuo Ohashi[12] and the IDEC-C2B8 Study Group[17]

[1]Department of Hematology, and Hematopoietic Stem Cell Transplantation, National Cancer Center Hospital, Tokyo; [2]Hematology/Oncology Division, Gunma Prefectural Cancer Center, Gunma; [3]Department of Breast Oncology and Hematology/Medical Oncology, National Cancer Center Hospital East, Chiba; [4]Department of Hematology, National Hospital Organization Hokkaido Cancer Center, Sapporo; [5]Department of Hematology, National Hospital Organization Nagoya Medical Center, Nagoya; [6]Department of Hematology and Chemotherapy, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka; [7]Department of Hematology and Oncology, Nagoya University Graduate School of Medicine, Nagoya; [8]Hematology/Oncology Division, National Hospital Organization Kyushu Cancer Center, Fukuoka; [9]Department of Hematology and Cell Therapy, Aichi Cancer Center, Nagoya; [10]Department of Radiology, International University of Health and Welfare Mita Hospital, Tokyo; [11]Department of Pathology, Teikyo University School of Medicine, Tokyo; [12]Biostatistics Sciences, School of Health Science and Nursing Biostatistics, University of Tokyo, Tokyo, Japan

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Information regarding rituximab monotherapy with eight weekly infusions for relapsed or refractory indolent B cell non-Hodgkin lymphoma (B-NHL), in particular for patients pretreated with rituximab, is limited. To evaluate the efficacy and safety of eight doses of rituximab monotherapy, 52 patients with relapsed or refractory indolent B-NHL were enrolled in the present study. Forty of 45 eligible patients (89%) had follicular lymphoma and 24 (53%) were at intermediate or high risk group according to the Follicular Lymphoma International Prognostic Index. The median number of prior chemotherapy regimens was 1 (range 1–7). At the median follow-up of 12.2 months, the overall response rate (ORR), complete response rate (%CR), and median progression-free survival (PFS) were 69% (95% confidence interval [CI] 53%–82%), 47% (95% CI 32%–62%), and 15.6 months (95% CI 10.6– months), respectively. In the 33 patients pretreated with rituximab, the ORR, %CR, and median PFS were inferior compared with values for the 12 patients who had not received rituximab previously (64% *vs* 83% for ORR; 39% *vs* 67% for %CR; and 13.8 *vs* 17.5 months for median PFS, respectively). All mild-to-moderate infusion-related toxicities were reversible. Grade 3/4 non-hematologic adverse events occurred in six of the 52 patients. Two patients developed Grade 4 late-onset neutropenia and a decrease (>50%) in serum immunoglobulin was observed in six patients. In conclusion, rituximab monotherapy with eight weekly infusions is effective in relapsed patients with indolent B-NHL, with acceptable toxicities, including in patients pretreated with rituximab; however, careful monitoring is recommended for infections associated with late-onset neutropenia and hypogammaglobulinemia. (University Hospital Medical Information Network no. UMIN000002974.) (*Cancer Sci* 2011; 102: 1698–1705)

Since the introduction of rituximab, a chimeric anti-CD20 mAb, into clinical trials and practice, it has been routinely used for the treatment of indolent and aggressive B cell non-Hodgkin lymphoma (B-NHL) in combination with chemotherapy, such as cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP), based on several Phase II and III studies.[1–5] However, in the treatment of indolent B-NHL, of which the most representative histopathologic subtype is follicular lymphoma, rituximab monotherapy has been regarded as a reasonable treatment option, especially for elderly patients with a low tumor burden, partly because indolent B-NHL is slow growing and is difficult to cure even with intensive chemotherapies.[3,6–8] In addition, rituximab monotherapy has often been applied to previously treated and untreated patients with indolent B-NHL[9–11] or as maintenance therapy after achieving remission.[12–16]

Rituximab monotherapy at doses of 375 mg/m^2 or slightly higher has been evaluated in Phase II studies with four weekly infusions for relapsed indolent B-NHL[9,10] and with eight weekly infusions for relapsed aggressive B-NHL;[17,18] however, information regarding rituximab monotherapy with eight weekly infusions for relapsed or refractory indolent B-NHL is limited to one previous report of a Phase II study in 37 patients who had not been pretreated with rituximab, in which a tendency for superior efficacy was found (overall response rate [ORR] 57% and median time to progression [TTP] in responders 19.4+ months)[19] compared with the four weekly infusion treatment regimen.[9,10]

In current clinical practice, retreatment with rituximab monotherapy with four weekly infusions is frequently used in patients with relapsed indolent B-NHL pretreated with rituximab.[20,21] However, there are no reports of rituximab retreatment with eight weekly infusions in this patient population. The aim of the present Phase II study was to investigate the outcome of eight weekly infusions of rituximab in patients with relapsed or refractory indolent B-NHL, mostly pretreated with rituximab.

[13]To whom correspondence should be addressed.
E-mail: ktobinai@ncc.go.jp
[14]Present address: Kenporen Osaka Central Hospital, Osaka, Japan.
[15]Present address: Department of Hematology and Cell Therapy, Aichi Cancer Center, Nagoya, Japan.
[16]Present address: Department of Hematology and Oncology, Nagoya Daini Red Cross Hospital, Nagoya, Japan.
[17]The participating institutions and principal investigators of the IDEC-C2B8 Study Group are: Hokkaido Cancer Center (M. Kurosawa and K. Aikawa), Sapporo Hokuyu Hospital (M. Kasai and Y. Kiyama), Tochigi Cancer Center (T. Izumi and Y. Kano), Gunma Cancer Center (T. Igarashi and K. Murayama), National Cancer Center Hospital East (K. Itoh), National Cancer Center Hospital (K. Tobinai, Y. Kobayashi, and T. Watanabe), Tokai University School of Medicine (T. Hotta and K. Ando), Aichi Cancer Center Hospital (Y. Morishima, M. Ogura, and K. Yamamoto), Nagoya University School of Medicine (T. Kinoshita, T. Murate, and H. Nagai), Nagoya Medical Center (H. Nagai and H. Ohashi), Kyoto Prefectural University of Medicine (M. Taniwaki), Center for Cardiovascular Diseases and Cancer, Osaka (A. Hiraoka and T. Karasuno), Hiroshima University School of Medicine (A. Sakai), National Kyushu Cancer Center (N. Uike).

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Our findings indicate that rituximab monotherapy with eight weekly infusions is safe and effective in this patient population.

Methods

Study design and endpoints. The present study was a single agent, multicenter, Phase II study. The primary endpoint was the ORR in all eligible patients. Secondary endpoints included progression-free survival (PFS) in all eligible and evaluable patients. The expected ORR (P_1) was set at 50% based on the preceding Phase II study for relapsed indolent B-NHL,[9,10] whereas the threshold ORR (P_0) was set at 30%. The number of patients required for the study was calculated as 44 ($\alpha = 0.05$ and $1 - \beta = 0.8$) according to Fleming's[22] two-stage testing procedure. Assuming that up to 15% of enrolled patients would be ineligible, we planned to enroll 52 patients. All patients were followed-up either until disease progression or for 24 months from the first infusion of rituximab as a protocol treatment.

Patient eligibility criteria. Patients with CD20-positive indolent B-NHL who had relapsed or were refractory to conventional chemotherapy with or without rituximab were eligible for inclusion in the study. The histopathology of the lymphoma was consistent with small lymphocytic lymphoma (SLL), lymphoplasmacytic lymphoma, splenic marginal zone lymphoma, extranodal marginal zone B cell lymphoma of mucosa-associated lymphoid tissue, nodal marginal zone B cell lymphoma or follicular lymphoma (Grades 1, 2, and 3), according to the World Health Organization (WHO) Classification, 3rd edition.[23] Transformed lymphomas from indolent B-NHL were excluded. Eligible patients had at least one measurable lesion exceeding 1.5 cm in largest diameter. The last chemotherapy cycle had to be completed at least 4 weeks prior to study entry. Previous rituximab administration had to be eight or fewer infusions. In patients who had received rituximab monotherapy or rituximab-containing chemotherapy as prior therapy, objective responses had to have been achieved. Patients were between 20 and 79 years of age and had an Eastern Cooperative Oncology Group (ECOG) performance status ≤2.[24] Patients had no other malignancies or serious infection, and had adequate organ function.

Patients meeting any one of the following criteria were excluded from the study: (i) a history of treatment with any mAb other than rituximab; (ii) a history of treatment with rituximab within 1 year prior to study entry; (iii) >5000/μL lymphoma cells in peripheral blood; (iv) symptomatic central nervous system (CNS) involvement or a history of CNS involvement of lymphoma; (v) seropositivity for hepatitis B virus surface antigen, hepatitis C virus antibody, human immunodeficiency virus, or human anti-chimeric antibody (HACA); and (vi) pregnancy or potential pregnancy. Patients who had received hematopoietic growth factors within 1 week prior to enrollment were also excluded from the study.

Each patient provided informed consent at the time of study entry. The study was approved by the institutional review board of each participating institution and was conducted in compliance with the Declaration of Helsinki.

Central pathology review. Unstained microscope slides of lymphoma tissues at initial diagnosis and/or at relapse were collected from each institution. In addition to H&E staining, immunohistochemical analyses were conducted using mAb, including an anti-CD20 mAb (L26), anti-CD3 mAb, anti-CD5 mAb, anti-CD10 mAb, anti-bcl-2 mAb, and anti-cyclin D1 mAb, as described previously.[25] Preparations were examined microscopically by a central pathology review committee composed of three hematopathologists.

Rituximab administration and premedication. Rituximab (IDEC-C2B8), manufactured by Genentech (South San Francisco, CA, USA), was supplied by Zenyaku Kogyo (Tokyo, Japan). The dosing schedule involved eight consecutive weekly infusions of 375 mg/m^2 rituximab. Patients were premedicated with 2 mg D-chlorpheniramine maleate and 400 mg acetaminophen 30 min prior to each infusion of rituximab. The rate of infusion was increased from 25 to 100 mg/h and then to 200 mg/h at 1 h intervals, based on the results of the preceding Phase I and II studies of rituximab monotherapy in Japan.[10,26]

Adverse events and adverse drug reactions. All adverse events (AE) associated with rituximab, or those for which the relationship with rituximab was unknown, were regarded as adverse drug reactions (ADR). The ADR were graded according to the toxicity criteria of the Japan Clinical Oncology Group,[27] an expanded version of the National Cancer Institute–Common Toxicity Criteria (version 2.0, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcv20_4-30-992.pdf, accessed Jun 21, 2011).

Serum rituximab and HACA levels. Serum concentrations of HACA were monitored before and after rituximab infusion using an ELISA, as described previously.[9,10,18,26] Serum rituximab concentrations were determined in 18 patients who signed another informed consent form for this pharmacokinetic (PK) study.[10,18,26] The PK parameters were calculated using WinNolin professional software (version 5.0.1; Pharsight, Mountain View, CA, USA).

Tumor response and PFS. Tumor lesions were observed by weekly physical examination during rituximab administration and using computed tomography (CT) scans approximately every 3 months thereafter. Response was assessed according to the International Workshop NHL Response Criteria.[28] In the present study, a CR was defined as the complete disappearance of all lesions and radiological or biological abnormalities and the absence of any new lesions. The term "CR unconfirmed" (CRu) was used to describe patients who met the criteria for a CR but who had an indeterminate bone marrow (BM) assessment or a >75% decrease from baseline in the sum of the products of the greatest perpendicular diameters (SPD) of all measurable lesions but with a residual mass. A partial response (PR) was defined as a >50% decrease from baseline in the SPD of all measured lesions, no increase in the size of any other lesions, and no new lesions. Stable disease (SD) was defined as neither a 50% decrease nor a 50% increase in the SPD of measured lesions; progressive disease (PD) was defined as the appearance of any new lesion or a >50% increase in the SPD from the nadir. In addition to efficacy evaluation at each participating institute, an independent third-party panel of three radiologists performed central evaluation using the CT films collected. The primary efficacy variable was the best ORR (the relative frequency of responders showing CR, CRu, or PR). Secondary efficacy variables included the CR rate (%CR) and PFS (defined as the time from the date of enrollment to the date of PD assessment or the date of death from any cause).

Statistical analyses. Response rates and 95% confidence intervals (CI) were calculated using Fisher's exact test. The median PFS (and 95% CI) was estimated using the Kaplan–Meier method[29] with the log-rank test.[30] In addition, pretreatment factors affecting ORR and PFS were analyzed. Factors selected for multivariate analyses included sex, age, Ann Arbor clinical stage,[31] Follicular Lymphoma International Prognostic Index (FLIPI),[32] pathology, lactate dehydrogenase (LDH), extranodal disease, BM involvement, tumor size, prior chemotherapy regimens, prior rituximab treatment, and duration of lymphoma. In multivariate analyses, a stepwise logistic regression model was used for factors affecting ORR and Cox's stepwise regression model was used for PFS. The relationship between PK parameters and response was analyzed using Student's *t*-test. All statistical analyses were performed with SAS version 9.1 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics. Fifty-two patients were enrolled in the study between October 2004 and March 2008 from 15 institutions across Japan. All 52 patients were confirmed to be CD20 positive, but the intensity of CD20 expression was not quantified by immunohistochemical staining. The major characteristics of all 52 patients and the 45 eligible patients at the time of enrollment are summarized in Table 1. One patient was ineligible for inclusion in the study because his lesion was judged non-malignant by the central pathology review. Another six patients were also deemed ineligible for inclusion in the study by the extramural review committee: two patients did not have any tumor lesions >1.5 cm; in one patient, the tumor had been measured by ultrasonography and not a CT scan at the time of enrollment; one patient had been treated with more than eight infusions of rituximab prior to study enrollment; one patient had not responded to previous chemotherapy containing rituximab; and one patient had a Grade 3 abnormality in serum potassium levels at the time of enrollment. Thus, 45 patients were judged eligible for inclusion in the study and their characteristics were similar to those of all 52 patients (Table 1). Thirty-three of the 45 eligible patients (73%) had been pretreated with rituximab monotherapy or in combination with chemotherapy.

Table 1. Patient characteristics

	Enrolled	Eligible
No. patients	52	45
No. women/men	27/25	23/22
Median (range) age (years)	60 (32–79)	62 (32–79)
Histopathology† (WHO)		
Follicular		
Grade 1 (*n*)	16	14
Grade 2 (*n*)	25	22
Grade 3a (*n*)	4	3
Grade 3b (*n*)	1	1
Nodal marginal zone (*n*)	4	4
Extranodal marginal zone (*n*)	1	1
Not evaluated (*n*)	1	0
Clinical stage at restaging (Ann Arbor) I–II/III–IV (*n*)	20/32	18/27
ECOG performance status 0–1/>1 (*n*)	52/0	45/0
B-symptoms absent/present (*n*)	51/1	44/1
No. nodal sites <4/>4	39/13	33/12
Bulky disease (>5 cm)	16	16
Extra nodal site absent/present (*n*)	40/12	35/10
Positive/negative BM involvement (*n*)	7/45	5/40
Serum LDH normal/elevated (*n*)	40/12	33/12
Follicular Lymphoma International Prognostic Index		
Low	26	21
Intermediate	17	15
High	9	9
Median (range) interval from the onset of symptoms (years)	4.7 (1.3–22.3)	4.8 (1.3–22.3)
Median (range) interval from the last therapy (years)	2.5 (0.1–13.8)	2.8 (0.1–13.8)
Prior therapy		
Surgery (*n*)	5	4
Radiotherapy (*n*)	12	11
Chemotherapy (*n*)	52	45
Median no. prior chemotherapy regimens (range)	1 (1–7)	1 (1–7)
Rituximab therapy (*n*)	38	33
Rituximab monotherapy (*n*)	7	5
Rituximab with chemotherapy (*n*)	31	28
Median no. (range) rituximab administrations	4 (3–12)	4 (3–8)
Median no. (range) relapses	1 (0–3)	1 (0–3)
Response to prior therapy		
Relapse/resistant	46/6	39/6

†Diagnoses were made by the central pathology review committee. WHO, World Health Organization; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase.

Early termination of rituximab treatment. Two patients discontinued rituximab treatment early before completion of the planned eight infusions. One patient withdrew consent after the sixth infusion of rituximab because of the occurrence of Grade 3 bronchospasm accompanied by dyspnea. Another patient was removed from the study by her investigator because her pre-existing Grade 3 hypokalemia had worsened to Grade 4 after the third infusion of rituximab.

Efficacy. Efficacy was evaluated in all 45 eligible patients as per the protocol.

ORR, complete response rate (%CR) and PFS. As indicated in Table 2, the ORR was 69% (31/45 patients; 95% CI 53%–82%), including a %CR of 47% (21/45 patients; 95% CI 32%–62%). Median PFS was 15.6 months at the median follow-up of 12.2 months (Fig. 1a).

Efficacy in patients with a prior history of rituximab treatment. Of the 45 eligible patients, 33 (73%) had a history of rituximab treatment at the time of study enrollment. Five had been pretreated with rituximab monotherapy and the remaining 28 had been pretreated with rituximab-containing chemotherapy. The median number of prior rituximab infusions was 4 (range 3–8). As indicated in Table 2 and Figure 1(b), the ORR, %CR, and PFS of patients who had been pretreated with rituximab exhibited a tendency towards inferior efficacy compared with those patients who had not been pretreated with rituximab, although the differences failed to reach statistical significance.

Table 2. Response and progression-free survival (*n* = 45)

	All eligible patients	Prior therapy	
		With rituximab	Without rituximab
No. patients evaluated	45	33	12
Response			
Complete response	13 (29%)	9 (27%)	4 (33%)
Complete response unconfirmed	8 (18%)	4 (12%)	4 (33%)
Partial response	10 (22%)	8 (24%)	2 (17%)
Stable disease	12 (27%)	10 (30%)	2 (17%)
Progression disease	1 (2%)	1 (3%)	0
Not evaluable	1 (2%)	1 (3%)	0
Overall response rate	31 (69%)	21 (64%)	10 (83%)
95% CI	53–82%	45–80%	52–98%
Progression-free survival			
Median (months)	15.6	13.8	17.5
95% CI	10.6–	9.7–	9.6–

The overall response rate (*P = 0.287, Fisher's exact test), complete response rate (†P = 0.176, Fisher's exact test) and progression-free survival (‡P = 0.372, log-rank test) were compared with those in patients who had not been treated with rituximab. Responses were evaluated according to the International Workshop NHL Response Criteria[28] and show the number of patients in each group with the percentage given in parentheses. The complete response rate consisted of the complete response rate plus the complete response unconfirmed rate. CI, confidence interval.

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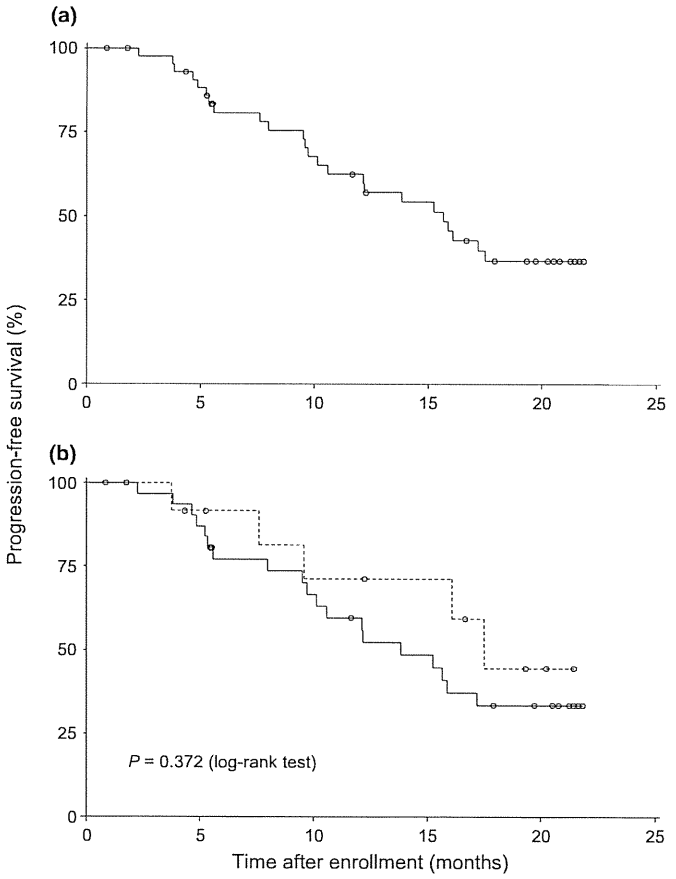

Fig. 1. Progression-free survival (PFS) curves for (a) all eligible patients at a median follow-up time of 12.2 months (median PFS 15.6 months; 95% confidence interval [CI] 10.6–; $n = 45$) and (b) patient groups who had either received prior rituximab therapy (——; $n = 33$; median PFS 13.8 months, 95% CI 9.7–) or not (- - - - -; $n = 12$; median PFS 17.5 months, 95% CI 9.6–). (○), censored.

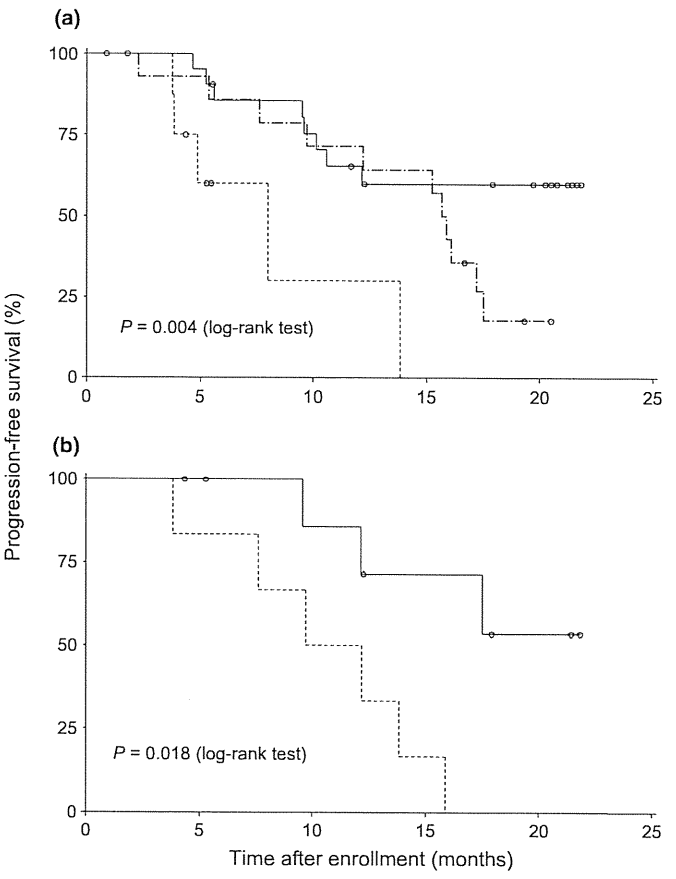

Fig. 2. Progression-free survival (PFS) curves for (a) patients categorized according to the Follicular Lymphoma International Prognostic Index as low risk (——; $n = 21$; median PFS not reached, 95% CI 10.6–), intermediate risk (– – – –; $n = 15$; median PFS 15.8 months, 95% CI 9.7–17.5), and high risk (·····; $n = 9$; median PFS 8 months, 95% CI 3.8–13.8), and (b) patient groups showing higher (maximum drug concentration [C_{max}] >450 μg/mL; ——; $n = 21$; median PFS not reached, 95% CI 12.1–) and lower (C_{max} ≤450 μg/mL; - - - - -; $n = 6$; median PFS 10.9 months, 95% CI 7.6–13.8) serum rituximab levels. (○), censored.

Factors affecting ORR and PFS. Univariate analysis revealed that PFS was significantly associated with FLIPI (Fig. 2a; $P = 0.004$, log-rank test). The median PFS of the low-risk FLIPI group was longer than that of the intermediate- and high-risk groups. Multivariate analysis of the 45 eligible patients indicated that advanced stage (III–IV) was an independent, unfavorable factor affecting ORR (odds ratio 6.623; 95% CI 1.021–43.478), whereas age (<60 years) and being in a higher risk FLIPI group (i.e. intermediate and high risk) were factors unfavorably affecting PFS (hazard ratio [HR] 4.651, 95% CI 1.218–17.857 for age; HR 7.684, 95% CI 1.992–29.647 for intermediate- and high-risk FLIPI groups).

Safety. Safety was evaluated in all 52 patients who received at least one infusion of rituximab. Grade 2 or greater toxicities relating to rituximab are listed in Table 3.

Hematologic toxicities. Of all 52 patients, 34 (65%) developed hematologic toxicities relating to rituximab. Leukopenia and neutropenia were observed in 27 (52%) and 20 patients (38%), respectively; however, cytopenias exceeding Grade 2 were not frequent, as indicated in Table 3. The neutropenia in 10 of the 20 patients occurred after completion of rituximab treatment. The median time from the last rituximab infusion to the documentation of neutropenia was 3.2 months (range 1.6–8.4 months).

Two patients developed Grade 4 neutropenia at 2.5 and 3.0 months after completion of rituximab therapy. These two patients recovered to the normal range or baseline without support by hematopoietic growth factors. One patient developed Grade 3 febrile neutropenia concomitant with Grade 4 viral enteritis 6.6 months after completion of the treatment protocol. Her neutrophil count recovered to the normal range 11 days after the initiation of supportive care.

Non-hematologic toxicities. Forty-nine of the 52 patients (94%) enrolled in the present study developed non-hematologic toxicities related to rituximab treatment, which were mostly infusion-related symptoms such as fever, chills, a burning sensation, headache, asthenia, pain, throat discomfort, perspiration, and pruritus and most of which did not exceed Grade 2. These symptoms generally appeared during the first infusion, decreased at subsequent infusions, and were effectively controlled within 24 h by prophylactic or supportive care with antihistamines and antipyretics.

Abnormal laboratory findings. Most laboratory abnormalities were of Grade 1, with Grade 2 or greater abnormalities rare (Table 3). Grade 4 elevation of liver enzymes (alanine aminotransferase, aspartate aminotransferase) was observed in one patient who developed viral hepatitis B (Table 4).

Infections. Eighteen episodes of infection were observed during the study period. Grade 2 or greater infections are listed in Table 3. Although one patient developed Grade 3 pneumonia

after the first rituximab infusion, the planned eight rituximab infusions were completed after recovery with supportive care. Two patients developed Grade 4 viral hepatitis B and Grade 3 viral enteritis at 6.3 and 6.6 months after the completion of eight rituximab infusions, respectively. Other infections were of Grade 1/2.

Table 3. Adverse drug reactions (≥Grade 2) in all 52 patients

	No. patients			Total ≥ Grade2 (%)
	Grade 2	Grade 3	Grade 4	
Hematologic toxicity				
Leukopenia	13	2	1	16 (31)
Neutropenia	4	1	2	7 (13)
Thrombocytopenia	1	1	0	2 (4)
Hemoglobin decreased	1	0	0	1 (2)
Non-hematologic toxicity				
Rash	5	0	0	5 (10)
Pruritus	5	0	0	5 (10)
Fever (pyrexia)	4	0	0	4 (8)
Urticaria	4	0	0	4 (8)
Diarrhea	3	0	0	3 (6)
Dizziness	2	0	0	2 (4)
Erythema	2	0	0	2 (4)
Weight loss	2	0	0	2 (4)
Abdominal pain	1	0	0	1 (2)
Acute pancreatitis	0	1	0	1 (2)
Anorexia	1	0	0	1 (2)
Bronchospasm	0	1	0	1 (2)
Chills	1	0	0	1 (2)
Constipation	1	0	0	1 (2)
Dyspnea	0	1	0	1 (2)
Dyspepsia	1	0	0	1 (2)
Eczema	1	0	0	1 (2)
Edema, eyelid	1	0	0	1 (2)
Febrile neutropenia	0	1	0	1 (2)
Hepatic cirrhosis	1	0	0	1 (2)
Nasal drainage	1	0	0	1 (2)
Oropharyngeal discomfort	1	0	0	1 (2)
Oropharyngeal pain	1	0	0	1 (2)
Phonation disorder	1	0	0	1 (2)
Rectosigmoid cancer	0	0	1	1 (2)
Stomatitis	1	0	0	1 (2)
Scrotal swelling	1	0	0	1 (2)
Tenderness	1	0	0	1 (2)
Vomiting	1	0	0	1 (2)
Abnormal laboratory findings				
Occult blood in urine	1	1	0	2 (4)
ALT increased	0	0	1	1 (2)
AST increased	0	0	1	1 (2)
Hyperbilirubinemia	0	0	1	1 (2)
Hyperkalemia	1	0	0	1 (2)
Hypoalbuminemia	1	0	0	1 (2)
Hypokalemia	0	1	0	1 (2)
Infections				
Bronchopneumonia	1	0	0	1 (2)
Hepatitis B	0	0	1	1 (2)
Herpes virus infection	1	0	0	1 (2)
Herpes zoster	1	0	0	1 (2)
Nasopharyngitis	1	0	0	1 (2)
Otitis media	1	0	0	1 (2)
Pneumonia	0	1	0	1 (2)
Viral enteritis	0	1	0	1 (2)

Fevers were axillary temperatures. The table includes all adverse drug reactions (ADR) that were probably or possibly related to rituximab. The ADR were graded according to the Japan Clinical Oncology Group (JCOG) Toxicity Criteria,[27] an expanded version of the NCI Common Toxicity Criteria (version 2.0).The ADR were documented at the highest grade throughout the study period. ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Grade 3/4 non-hematologic AE. The Grade 3/4 non-hematologic AE in six patients are given in Table 4. Three patients developed pneumonia, viral enteritis, and hepatitis B infections. Although one other patient developed Grade 3 bronchospasm with dyspnea after the sixth rituximab infusion, it was manageable with supportive care. Another patient developed Grade 3 acute pancreatitis at 6.5 months after completion of rituximab treatment. The patient recovered 12 days later. In addition, one patient developed rectosigmoid cancer 9.4 months after completion of rituximab treatment, which was managed by surgical resection. This patient showed neither clinical signs nor radiographic abnormalities suggestive of malignancy in the lower abdomen at the time of study entry. Nine months after the last rituximab infusion, the patient was found to have an intestinal obstruction suggestive of colon cancer and was hospitalized for a colectomy. Histopathological examination revealed tubular adenocarcinoma in the rectosigmoid junction. The relationship between the development of this rectosigmoid carcinoma and rituximab is unknown.

Other pharmacological findings. *T and B cell counts in peripheral blood.* All patients exhibited a marked decrease in $CD19^+$ and $CD20^+$ cells after the first rituximab infusion. The decrease lasted for 3 months and recovered gradually from 6 months or later, except in one patient. None of the patients was found to have HACA.

Serum immunoglobulins. A decrease in serum immunoglobulins (IgA, IgM, or IgG) to ≤50% than baseline was observed in six patients. The time course of changes in serum immunoglobulin levels is given in Table 5.

Serum rituximab levels and correlation with PFS. Serum rituximab levels in 15 patients who received eight infusions increased cumulatively, but did not reach a steady state. There were no significant differences in serum rituximab levels between responders and non-responders, and no correlations

Table 4. Grade 3/4 non-hematologic adverse events

Patient no./toxicity	Grade	Onset
Patient 2		
Pneumonia	3	Cycle 1 (Day 7)
Patient 3		
Bronchospasm	3	Cycle 6 (during infusion)
Dyspnea	3	
Patient 13		
Febrile neutropenia	3	Day 201 after completion of Cycle 8
Viral enteritis	3	
Patient 21		
Acute pancreatitis	3	Day 197 after completion of Cycle 8
Patient 43		
Rectosigmoid cancer	4	Day 287 after completion of Cycle 8
Patient 44		
Hepatitis B accompanied by Grade 4 increases in AST and ALT	4	Day 193 after completion of Cycle 8

The table includes all Grade 3/4 non-hematologic adverse events (AE) that were probably or possibly related to rituximab. The AE were graded according to the Japan Clinical Oncology Group (JCOG) Toxicity Criteria,[27] an expanded version of the NCI Common Toxicity Criteria (version 2.0). The AE were documented at the highest grade throughout the study periods. ALT, alanine aminotransferase; AST, aspartate aminotransferase.

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between PK parameters and ORR. However, PFS in patients showing a higher maximum drug concentration (C_{max}) of rituximab (>450 μg/mL) was longer than that in patients with a lower C_{max} (Fig. 2b; $P = 0.018$, log-rank test).

Discussion

The present Phase II study revealed that rituximab monotherapy with eight weekly infusions is safe and effective in patients with relapsed indolent B-NHL, including those who have been pretreated with rituximab. An analogous eight-dose rituximab Phase II study was conducted in relapsed patients with indolent B-NHL who had not been pretreated with rituximab by Piro *et al.* in the US.[19] The ORR in the present study was comparable to that reported in the US study (69% *vs* 60%), whereas the %CR in the present study was higher than that in the US study (47% *vs* 14%). These differences may be explained, in part, by differences in the response criteria and patient characteristics, including histopathologic subtypes, such as SLL. Regarding Grade 2 or greater AE, there were no clinically relevant differences between the two studies, except for slightly more frequent skin reactions (rash, pruritus, and urticaria) in the present study. Previously, we have conducted three rituximab monotherapy studies in Japan.[10,18,21] There appear to be no differences between the Japanese studies and those from Western countries in terms of efficacy and safety,[9,10,33,34] suggesting no ethnic-related differences in responses to rituximab monotherapy.

In the present study, the efficacy of rituximab monotherapy in patients who had been pretreated with rituximab tended to be inferior compared with efficacy in patients without a history of rituximab treatment, as evidenced by ORR, %CR, and PFS, although these differences failed to reach statistical significance. It has been reported previously that prior rituximab treatment is an unfavorable prognostic factor in patients with diffuse large B cell lymphoma who receive salvage chemotherapy at relapse.[35,36] In addition, a maintenance study involving follicular lymphoma found that the improvements in the OS and PFS of a patient group whose remission was induced with cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab (R-CHOP) were both less than those of a patient group whose remission was induced with CHOP.[13,37] Nevertheless, the efficacy results of rituximab monotherapy with eight weekly infusions in patients pretreated with rituximab (ORR 64%, %CR 39%, and median PFS 13.8 moths) still compared favorably with efficacy in patients that had not been pretreated[9,10] and in patients pretreated with four weekly rituximab infusions.[20,21] Although the exact reasons for the relatively high efficacy in patients pretreated with rituximab in the present study are unknown, they may be explained, in part, by the extended eight weekly rituximab infusions. Considering these results, rituximab monotherapy with eight weekly infusions is a reasonable therapeutic option for this patient population.

The frequency and severity of the AE observed in the present study appeared to be slightly higher than in our previous on relapsed indolent B-NHL,[10] which consisted of only four rituximab infusions rather than the eight used in the present study, and were almost equivalent to those in aggressive B-NHL.[18] In addition to the extension of rituximab dosing, shorter monitoring intervals may be responsible for the higher frequency and severity of AE in the present study. One of the notable findings of the present study is the relatively frequent observation of late-onset neutropenia and hypogammaglobulinemia. Of the 20 patients who developed neutropenia, half ($n = 10$) developed it after completion of the treatment protocol (onset 1.6–8.4 months after completion of treatment). Although Grade 4 neutropenia was observed in two of the 10 patients, these two patients did not suffer from severe infections. In six patients, serum immunoglobulin levels were decreased to <50% of each baseline level. In particular, there was a marked decrease in IgM and this decrease was seen in all six patients. One of the six patients who concomitantly developed Grade 3 febrile late-onset neutropenia also developed Grade 4 viral enteritis, whereas no infectious episode was observed in the remaining five patients. Such a marked decrease in serum immunoglobulin levels was not observed in our previous four-dosing monotherapy study of relapsed indolent B-NHL,[10] whereas similar tendencies were observed in a previous eight-dosing rituximab monotherapy study in aggressive B-NHL.[18] Although rituximab monotherapy is a reasonable treatment option for patients with untreated or treated indolent B-NHL, especially for elderly patients with a

Table 5. Serum immunoglobulin levels

Patient no.	No. prior rituximab administrations	Response		Treatment period (weeks)					
				Baseline	12–23	24–35	36–47	48–71	72–96
5 (male)	6	PR	IgG (mg/dL)	380	358	325	283	207	152
			% Decrease from baseline	–	6	14	26	46	60
			IgM (mg/dL)	22	6	≤5	≤5	≤5	≤5
			% Decrease from baseline	–	73	≤77	≤77	≤77	≤77
			IgA (mg/dL)	128	94	90	76	65	49
			% Decrease from baseline	–	27	30	41	49	62
13 (female)	0	NE	IgM (mg/dL)	47	25	21	25	30	–
			% Decrease from baseline	–	47	55	47	36	–
			IgA (mg/dL)	97	63	49	46	47	–
			% Decrease from baseline	–	35	49	53	52	–
16 (male)	4	NE	IgM (mg/dL)	23	12	14	10	18	–
			% Decrease from baseline	–	48	39	57	22	–
22 (male)	0	CRu	IgM (mg/dL)	92	28	–	17	–	14
			% Decrease from baseline	–	70	–	82	–	85
23 (male)	8	CR	IgM (mg/dL)	46	28	–	19	18	–
			% Decrease from baseline	–	39	–	59	61	–
25 (male)	4	CR	IgM (mg/dL)	85	41	34	–	–	35
			% Decrease from baseline	–	52	60	–	–	59

Normal ranges are: 870–1700 mg/dL for IgG; 46–260 and 33–190 mg/dL for IgM in women and men, respectively; and 110–410 mg/dL for IgA. The table includes values that markedly decreased (>50%) compared with the baseline. CR, complete response; CRu, complete response unconfirmed; NE, not evaluable.

low tumor burden, careful monitoring for infections and secondary malignancy is required.

In conclusion, rituximab monotherapy with eight weekly infusions is safe and effective in patients with relapsed or refractory indolent B-NHL, including those who have been pretreated with rituximab, suggesting that this therapy is a reasonable option for this patient population. However, careful monitoring is recommended for infections associated with late-onset neutropenia and hypogammaglobulinemia.

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