Kakugawa Y, Terasaka S, Watanabe T, Tanaka S, Taniguchi H, Saito Y.	Enteropathy-associated T-cell lymphoma in small intestine detected by capsule endoscopy.	Leuk Lymphoma		in press.	2012
Fukuhara S, Watanabe T, Munakata W, Mori M, Maruyama D, Kim SW, Kobayashi Y, Taniguchi H, Maeshima AM, Tanosaki R, Matsuno Y, Tobinai K.	Bulky disease has an impact on outcomes in primary diffuse large B-cell lymphoma of the breast: a retrospective analysis at a single institution.	Eur J Haematol.	87(5)	434-440	2011
Tomita N, Yokoyama M, Yamamoto W, Watanabe R, Shimazu Y, Masaki Y, Tsunoda S, Hashimoto C, Murayama K, Yano T, Okamoto R, Kikuchi A, Tamura K, Sato K, Sunami K, Shibayama H, Takimoto R, Ohshima R, Hatta Y, Moriuchi Y, Kinoshita T, Yamamoto M, Numata A, Ishigatsubo Y, Takeuchi K.	Central nervous system event in patients with diffuse large B-cell lymphoma in the rituximab era.	Cancer Sci.	103(2)	245-251	2012
Takahashi H, Tomita N, Yokoyama M, Tsunoda S, Yano T, Murayama K, Hashimoto C, Tamura K, Sato K, Ishigatsubo Y.	Prognostic impact of extranodal involvement in diffuse large B-cell lymphoma in the rituximab era.	Cancer	2011 Dec 27. doi: 10.1002/cncr.27381. [Epub ahead of print]		2011
Nishimura N, Nakano K, Ueda K, Kodaira M, Yamada S, Mishima Y, Yokoyama M, Terui Y, Takahashi S, Hatake K.	Prospective evaluation of incidence and severity of oral mucositis induced by conventional chemotherapy in solid tumors and malignant lymphomas.	Support Care Cancer	2011 Nov 25. [Epub ahead of print]		2011
Suzuki K, Terui Y, Nakano K, Nara E, Nasu K, Ueda K, Nishimura N, Mishima Y, Sakajiri S, Yokoyama M, Takahashi S, Hatake K.	High thymidine kinase activity is a strong predictive factor for poor prognosis in PTCLs treated by CHOP.	Leuk Lymphoma	2011 Oct 31. [Epub ahead of print]		2011
牛島洋子、山本一仁	T 細胞性リンパ系腫瘍に対する新規薬剤の導入による新たな治療展開.【注目される造血器腫瘍に対する新規薬剤の現状と展望】	血液内科	62(1)	51-57	2011

山本一仁	高リスクびまん性大細胞型 B 細胞リンパ腫：R-CHOP を越える治療の動向．特集「B 細胞リンパ腫治療のパラダイムシフト」	血液フロンティア	21(10)	77(1457)-86(1466)	2011
稲垣裕一郎、山本一仁	白血病に対する個別化治療．特集「標準治療となった個別化治療	腫瘍内科	9(1)	50-58	2012
山本一仁	Upfront 自家移植の評価．特集「造血器腫瘍における高用量治療の評価」	腫瘍内科	9(2)	137-145	2012
糸永英弘、福島卓也、田口潤、今西大介、今泉芳孝、波多智子、塚崎邦弘、宮崎泰司	顆粒リンパ球増多症に続発した急性単芽球性白血病.	臨床血液	52(12)	1870-1875	2011
鵜池直邦	疾患各論　慢性リンパ性白血病	クリニシアン	Vol.58 No.595	179-184	2011
崔日承、鵜池直邦	成人 T 細胞白血病リンパ腫に対するミニ移植の有効性は持続するか？	血液内科	63	46-50	2011
岩下生久子、井野彰浩、鵜池直邦、内田耕栄、西牟田雄祐、上原智	HTLV-1 感染者の上部消化管病変.	胃と腸	46	264-274	2011
鵜池直邦	トレアキシン治療のワンポイント解析『治療中留意すべき副作用・臨床症状の発現時期解析』	Clinical Management シリーズ			2011
宇都宮與、石田高司、鵜池直邦、瀬戸加大.	Round Table Discussion 成人 T 細胞白血病研究の進歩と今後の展望	Trends in Hematological Malignancies	Vol3 No.2,	64-71,	2011
鵜池直邦	「がん診療に携わる全ての医師のための心のケアガイド」を読んで	JPOS News Letter	no.66		2011
小畠勝己、竹下盛重、松本慎二、神原　豊、大神明子、鍋島一樹、西山尚子、鵜池直邦、宮久　禎、中島　豊	乳腺原発の悪性リンパ腫の 13 例における細胞学的および免疫組織化学の検討	J Jpn Soc. Clin. Cytol.	50	270-278	2011

Ⅳ．研究成果の刊行物・別刷

VOLUME 30 · NUMBER 8 · MARCH 10 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Defucosylated Anti-CCR4 Monoclonal Antibody (KW-0761) for Relapsed Adult T-Cell Leukemia-Lymphoma: A Multicenter Phase II Study

Takashi Ishida, Tatsuro Joh, Naokuni Uike, Kazuhito Yamamoto, Atae Utsunomiya, Shinichiro Yoshida, Yoshio Saburi, Toshihiro Miyamoto, Shigeki Takemoto, Hitoshi Suzushima, Kunihiro Tsukasaki, Kisato Nosaka, Hiroshi Fujiwara, Kenji Ishitsuka, Hiroshi Inagaki, Michinori Ogura, Shiro Akinaga, Masao Tomonaga, Kensei Tobinai, and Ryuzo Ueda

Takashi Ishida, Hiroshi Inagaki, and Ryuzo Ueda, Nagoya City University Graduate School of Medical Sciences; Kazuhito Yamamoto, Aichi Cancer Center; Michinori Ogura, Nagoya Daini Red Cross Hospital, Nagoya; Tatsuro Joh and Masao Tomonaga, Japanese Red Cross Nagasaki Genbaku Hospital; Shinichiro Yoshida, Nagasaki Medical Center; Kunihiro Tsukasaki, Atomic Bomb Disease Institute, Nagasaki University Graduate School of Biomedical Science, Nagasaki; Naokuni Uike, National Kyushu Cancer Center; Toshihiro Miyamoto, Kyushu University Graduate School of Medical Sciences; Kenji Ishitsuka, Fukuoka University School of Medicine, Fukuoka; Atae Utsunomiya, Imamura Bun-in Hospital, Kagoshima; Yoshio Saburi, Oita Prefectural Hospital, Oita; Shigeki Takemoto, Kumamoto Medical Center; Hitoshi Suzushima, NTT West Japan Kyushu Hospital; Kisato Nosaka, Kumamoto University Hospital, Kumamoto; Hiroshi Fujiwara, Ehime University Graduate School of Medicine, Ehime; Shiro Akinaga, Kyowa Hakko Kirin; and Kensei Tobinai, National Cancer Center Hospital, Tokyo, Japan.

Submitted June 3, 2011; accepted December 5, 2011; published online ahead of print at www.jco.org on February 6, 2012.

Supported by Kyowa Hakko Kirin (Tokyo, Japan).

Presented in part at the 52nd Annual Meeting of the American Society of Hematology, December 4-7, 2010, Orlando, FL.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical Trials repository link available on JCO.org.

Corresponding author: Takashi Ishida, MD, PhD, Department of Medical Oncology and Immunology, Nagoya City University Graduate School of Medical Sciences, 1 Kawasumi, Mizuho-chou, Mizuho-ku, Nagoya, Aichi, 467-8601, Japan; e-mail: itakashi@med.nagoya-cu.ac.jp.

0732-183X/12/3008-837/$20.00

DOI: 10.1200/JCO.2011.37.3472

ABSTRACT

Purpose
Adult T-cell leukemia-lymphoma (ATL) is usually resistant to conventional chemotherapies, and there are few other treatment options. Because CC chemokine receptor 4 (CCR4) is expressed on tumor cells from most patients with ATL, KW-0761, a humanized anti-CCR4 monoclonal antibody, which markedly enhances antibody-dependent cellular cytotoxicity, was evaluated in the treatment of patients with relapsed ATL.

Patients and Methods
A multicenter phase II study of KW-0761 for patients with relapsed, aggressive CCR4-positive ATL was conducted to evaluate efficacy, pharmacokinetic profile, and safety. The primary end point was overall response rate, and secondary end points included progression-free and overall survival from the first dose of KW-0761. Patients received intravenous infusions of KW-0761 once per week for 8 weeks at a dose of 1.0 mg/kg.

Results
Of 28 patients enrolled onto the study, 27 received at least one infusion of KW-0761. Objective responses were noted in 13 of 26 evaluable patients, including eight complete responses, with an overall response rate of 50% (95% CI, 30% to 70%). Median progression-free and overall survival were 5.2 and 13.7 months, respectively. The mean half-life period after the eighth infusion was 422 ± 147 hours (± standard deviation). The most common adverse events were infusion reactions (89%) and skin rashes (63%), which were manageable and reversible in all cases.

Conclusion
KW-0761 demonstrated clinically meaningful antitumor activity in patients with relapsed ATL, with an acceptable toxicity profile. Further investigation of KW-0761 for treatment of ATL and other T-cell neoplasms is warranted.

J Clin Oncol 30:837-842. © 2012 by American Society of Clinical Oncology

INTRODUCTION

Adult T-cell leukemia-lymphoma (ATL) is an aggressive peripheral T-cell neoplasm caused by human T-cell lymphotropic virus type I. The disease is resistant to conventional chemotherapeutic agents, and there currently exist limited treatment options; thus, it has a poor prognosis.[1-4] A recent phase III trial for previously untreated patients with aggressive ATL (acute, lymphoma, or unfavorable chronic type) age 33 to 69 years demonstrated that a dose-intensified multidrug regimen, VCAP-AMP-VECP (vincristine, cyclophosphamide, doxorubicin, and prednisone; doxorubicin, ranimustine, and prednisone; and vindesine, etoposide, carboplatin, and prednisone), resulted in median progression-free (PFS) and overall survival (OS) of 7.0 and 12.7 months, respectively.[5] This remains unsatisfactory compared with responses in other hematologic malignancies. Allogeneic hematopoietic stem-cell transplantation has evolved into a potential approach to treating patients with ATL over the last decade. However, only a small fraction of patients with ATL have the opportunity to benefit from transplantation, such as those who are younger, have achieved sufficient disease control, and have an appropriate stem-cell source.[6,7] Therefore, the development of alternative treatment strategies for patients with ATL is an urgent issue.

Because CC chemokine receptor 4 (CCR4) is expressed on tumor cells from most patients with ATL,[8,9] we postulated that it might represent a novel molecular target for immunotherapy. Accordingly, KW-0761, a next-generation humanized anti-CCR4 immunoglobulin G1 (IgG1) monoclonal antibody (mAb) with a defucosylated Fc region, which markedly enhances antibody-dependent cellular cytotoxicity (ADCC), was developed.[10,11] We demonstrated that robust ADCC by the defucosylated anti-CCR4 mAb against primary tumor cells from patients with ATL mediated by autologous effector cells was triggered both in vitro and in a humanized mouse model in vivo.[11-13] These promising preclinical results prompted us to conduct a phase I clinical trial of KW-0761 for patients with relapsed CCR4-positive peripheral T-cell lymphoma (PTCL), including ATL. This study demonstrated good tolerability, predictable pharmacokinetics, and preliminary evidence of potent antitumor activity and resulted in a recommended dose of 1.0 mg/kg for subsequent clinical trials.[14] Herein, we report the results of a multicenter phase II study designed to assess the efficacy, pharmacokinetic profile, and safety of KW-0761 monotherapy in patients with relapsed CCR4-positive aggressive ATL.

PATIENTS AND METHODS

Patients

Patients 20 years of age or older with CCR4-positive aggressive ATL (acute, lymphoma, or unfavorable chronic type)[1,4] who had relapsed after at least one prior chemotherapy regimen were eligible. The unfavorable chronic type of ATL was defined by the presence of at least one of the following three factors: low serum albumin, high lactate dehydrogenase, or high blood urea nitrogen concentration.[5] CCR4 expression was determined by immunohistochemistry or flow cytometry using a mouse anti-CCR4 mAb (KM2160)[8,14] and confirmed by a central review committee. All patients were required to have an Eastern Cooperative Oncology Group performance status of 0 to 2. Eligibility criteria also included the following laboratory values: absolute neutrophil count $\geq$ 1500/μL, platelet count $\geq$ 50,000/μL, hemoglobin $\geq$ 8.0 g/dL, AST $\leq$ 2.5 $\times$ the upper limit of the normal range (UNL), ALT [lteuq] 2.5 $\times$ UNL, total bilirubin $\leq$ 1.5 $\times$ UNL, serum creatinine $\leq$ 1.5 $\times$ UNL, corrected serum calcium $\leq$ 11.0 mg/dL, and arterial partial oxygen pressure $\geq$ 65 mmHg or arterial blood oxygen saturation $\geq$ 93%. Patients were excluded if they had an active infection, a history of organ transplantation, active concurrent cancers, CNS involvement, a bulky mass requiring emergent radiotherapy, or seropositivity for hepatitis B virus antigen, hepatitis C virus antibody, or HIV antibody.

Study Design

This study was a multicenter, single-arm, phase II trial. Objectives of the study were to evaluate the efficacy, pharmacokinetic profile, and safety of KW-0761 monotherapy. Patients received intravenous infusions of KW-0761 once per week for 8 weeks at a dose of 1.0 mg/kg.[14] Oral antihistamine and acetaminophen were administered before each KW-0761 infusion to prevent infusion reactions. The primary end point was overall response rate (ORR), and secondary end points included the best response by disease site, PFS, and OS. Objective responses were assessed after the fourth and eighth infusions of KW-0761 by an independent efficacy assessment committee according to the modified response criteria for ATL.[4] It was estimated that 25 patients would be required to detect a lower limit of the 95% CI exceeding the 5% threshold of ORR based on the assumptions that the minimum required ORR for a new drug for relapsed, aggressive ATL is 5%,[15] with an expected ORR for KW-0761 of 30%[14] with 90% power. Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for AEs, version 3.0. The presence of human anti-KW-0761 antibodies in the patients' plasma was examined using enzyme-linked immunosorbent assay. Blood samples collected at times strictly in accordance with the protocol were employed for the pharmacokinetic analysis. Samples were obtained from patients who had received at least one dose of KW-0761 up to all eight doses. When any event resulted in an alteration in the infusion protocol, only those samples taken before the alteration were used for the analysis. The following parameters were calculated for plasma KW-0761: maximum drug concentration and trough drug concentration of each KW-0761 administration, area under the blood concentration time curve from 0 to 7 days after the first and eighth doses, and half-life period ($t_{1/2}$) after the eighth dose. As an additional research parameter, we investigated blood T-cell subset distribution during and after KW-0761 treatment and compared these values with those of 10 healthy donors as controls (five men, five women; median age, 45 years; range, 41 to 57 years).

Statistical Analysis

Survival estimates were calculated using the Kaplan-Meier method. PFS was defined as the time from the first dose of KW-0761 to progression, relapse, or death resulting from any cause, whichever occurred first. OS was measured from the day of the first dose to death resulting from any cause. Regarding T-cell subset analysis, differences between the patients' values before KW-0761 treatment and those of the controls were examined using the Mann-Whitney U-test. Differences between KW-0761 pretreatment values and those at each time point after KW-0761 treatment were examined using the Wilcoxon signed-rank test. All analyses were performed with SPSS Statistics 17.0 (SPSS, Chicago, IL). In this study, $P < .05$ was considered significant.

Study Oversight

The study was sponsored by Kyowa Hakko Kirin Company (Tokyo, Japan). The academic investigators and the sponsor were jointly responsible for the study design. The protocol was approved by the institutional review board at each participating site, and all patients and controls provided written informed consent before enrollment according to the Declaration of Helsinki.

RESULTS

Patients

Of the 28 patients enrolled onto the study, 27 (12 men, 15 women) received at least one infusion of KW-0761. One patient was withdrawn for aggravation of the general condition before the administration of KW-0761. Demographics and clinical characteristics of the 27 patients are summarized in Table 1. Median age was 64 years (range, 49 to 83). The disease subtypes included 14 acute, six lymphoma, and seven unfavorable chronic type ATL. Of these 27 patients, 14 (52%) completed the schedule of eight planned infusions. Of the remaining 13 patients, 11 (41%) discontinued treatment because of disease progression, one (4%) because of skin rash, and another (4%) because of concurrent colon cancer, for which this patient was excluded from the efficacy evaluation.

Efficacy of KW-0761

Of 26 patients evaluable for efficacy, objective responses were noted in 13 patients (ORR, 50%; 95% CI, 30% to 70%), including eight complete responses (CRs). Responses according to disease site were 100% (13 of 13; all CRs) for blood, 63% (five of eight) for skin, and 25% (three of 12) for nodal and extranodal lesions. Responses according to disease subtype were 43% (six of 14) for acute, 33% (two of six) for lymphoma, and 83% (five of six) for unfavorable chronic type ATL. Responses according to number of prior chemotherapy regimens were 48% (10 of 21) in those who had one prior regimen and 60% (three of five) for those who had two or three prior regimens. Median PFS and OS were 5.2 and 13.7 months, respectively (Figs 1A, 1B).

Table 1. Patient Demographics and Clinical Characteristics (n = 27)*

Characteristic	No.	%
Age, years		
Median	64	
Range	49-83	
≥ 65	13	48
Sex		
Male	12	44
Female	15	56
ECOG performance status†		
0	15	56
1	7	26
2	5	19
Disease subtype		
Acute	14	52
Lymphoma	6	22
Chronic	7	26
Prior chemotherapy regimens, No.		
1	22	82
2	3	11
3	2	7

Abbreviation: ECOG, Eastern Cooperative Oncology Group.
*Of 28 patients enrolled, 27 received at least one infusion of KW-0761.
†ECOG performance status scores range from 0 (normal activity) to 5 (death), with higher scores indicating more severe disability.

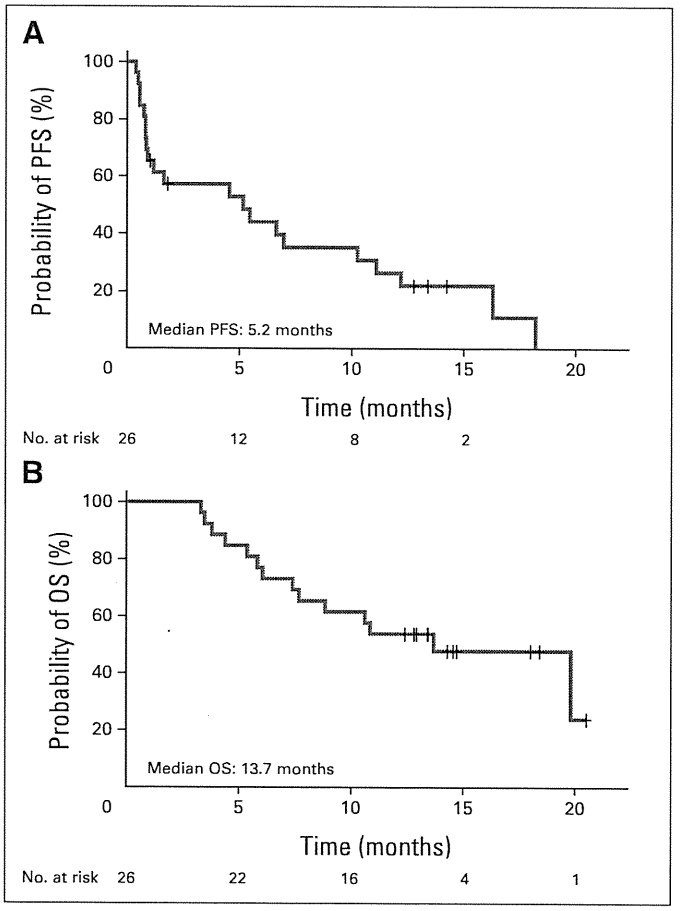

Fig 1. Kaplan-Meier curves of estimated (A) progression-free survival (PFS; median, 5.2 months) and (B) overall survival (OS; median, 13.7 months).

Pharmacokinetics

KW-0761 plasma concentrations over eight infusions, once per week, at 1.0 mg/kg are shown in Figure 2. Mean maximum drug concentration and trough drug concentration (± standard deviation) of the eighth infusion were 42.9 ± 14.2 μg/mL and 33.6 ± 10.6 μg/mL, respectively. Mean area under the blood concentration time curve from 0 to 7 days after the eighth infusion was 6,297 ± 1,812 μg × hours/mL. The mean $t_{1/2}$ after the eighth infusion was 422 ± 147 hours.

AEs

Table 2 lists AEs that occurred in at least 15% of patients or at grades 3 to 4, which were determined as possibly, probably, or definitely KW-0761 related. The most common nonhematologic AE was an infusion reaction (89%). In addition, 80% or more of the following recorded AEs occurred along with an infusion reaction: fever, chills, tachycardia, hypertension, nausea, and hypoxemia (Table 2). These events occurred primarily at the first infusion, becoming less frequent with subsequent treatments. The infusion reactions and component events were transient, and all patients recovered, although some needed systemic steroids. Skin rashes were observed as another frequent nonhematologic AE (63%), mostly occurring after the fourth or subsequent infusions. Of the 14 patients who developed grade 2 or higher skin rashes, objective responses were noted in 13 patients (93%), including eight CRs. On the other hand, of the 12 patients who developed no or grade 1 skin rashes, no objective responses were observed. A typical clinical course of the rash is depicted in Appendix Figures A1A and A1B (online only). The skin rash observed in this patient appeared after the seventh infusion, and the corresponding skin biopsy revealed mild perivascular CD8-positive cells dominating an inflammatory reaction, with an absence of ATL cells. The skin rash recovered on application of topical steroid. Of the 17 patients who developed skin rashes, one developed Stevens-Johnson syndrome, which was determined as possibly KW-0761 related, although that patient also received trimethoprim/sulfamethoxazole, fluconazole, and acyclovir for prevention of infection according to the protocol. This patient stopped those preventive agents and was treated with

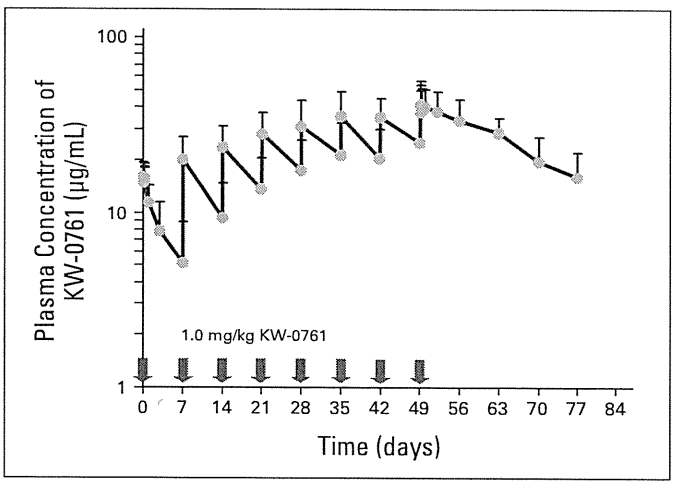

Fig 2. Pharmacokinetics of KW-0761. Mean KW-0761 plasma concentrations during and after 1.0 mg/kg KW-0761 infusions once per week for 8 weeks. Bar indicates upper limit of standard deviation.

Table 2. Adverse Events (n = 27)*

Adverse Event	Grade (No. of patients) 1	2	3	4	All Grades No. of Patients	%	Infusion Reaction Related (No. of patients) All Grades	≥ Grade 2
Nonhematologic								
Infusion reaction	1	22	1	0	24	89		
Fever	20	2	0	0	22	82	18	2
Rash	3	9	5	0	17	63	1	0
Chills	14	2	0	0	16	59	16	2
ALT	5	4	2	0	11	41		
AST	3	5	2	0	10	37		
Tachycardia	9	0	0	0	9	33	9	0
Hypertension	6	2	0	0	8	30	8	1
Albuminemia	7	1	0	0	8	30		
ALP	4	2	0	0	6	22		
Weight gain	5	0	0	0	5	19		
Nausea	4	1	0	0	5	19	5	1
Hyponatremia	5	0	0	0	5	19		
Hypoxemia	0	2	3	0	5	19	4	4
Hypotension	2	2	0	0	4	15	3	1
Pruritus	0	3	1	0	4	15		
γ-GTP	0	1	3	0	4	15		
Hypophosphatemia	0	4	0	0	4	15		
Hyperuricemia	4	0	0	0	4	15		
Hypercalcemia	1	1	0	1	3	11		
Hypokalemia	1	0	2	0	3	11		
Erythema multiforme†	0	0	1	0	1	4		
Hyperglycemia	0	0	1	0	1	4		
Tumor lysis syndrome	0	0	1	0	1	4		
Metabolic/laboratory, other‡	4	7	3	0	14	52		
Hematologic								
Lymphopenia§	0	6	9	11	26	96		
Leukocytopenia	3	7	8	0	18	67		
Thrombocytopenia	7	2	3	2	14	52		
Neutropenia	5	4	5	0	14	52		
Hemoglobin	4	3	1	0	8	30		

Abbreviations: ALP, alkaline phosphatase; BUN, blood urea nitrogen; CRP, C-reactive protein; GTP, glutamyl transpeptidase.

*Of 28 patients enrolled, 27 received at least one infusion of KW-0761. Listed are adverse events determined as possibly, probably, or definitely KW-0761 related that occurred in at least 15% of patients or were of grade 3 to 4 severity.

†One patient diagnosed as having Stevens-Johnson syndrome.

‡Other metabolic and laboratory test abnormalities included hypoproteinemia, BUN elevation, CRP, glycosuria, hypochloremia, and hyperammoniemia.

§Lymphopenia included decrease of abnormal lymphocytes.

systemic steroids, but improvement required the passage of 4 months. Lymphopenia, including a decrease in the number of ATL cells, occurred in 26 (96%) of the 27 patients. Grades 3 to 4 thrombocytopenia was observed in five patients (19%) but was not associated with bleeding, and grade 3 neutropenia also occurred in five patients but did not lead to a febrile episode. The latter two hematologic AEs improved in all patients. None of the patients developed detectable anti–KW-0761 antibody.

T-Cell Subset Analysis

The numbers of circulating blood CD4+ CCR4+, CD4+ CD25+ FOXP3+, CD4+ CCR4−, and CD4− CD8+ cells from KW-0761–treated patients and those from the 10 controls are presented as box and whisker plots in each graph (Appendix Figs A2A to A2D, online only). The numbers of CD4+ CCR4+ and CD4+ CD25+ FOXP3+ cells in patients with ATL before treatment were significantly higher than those in the controls but were significantly reduced after the first KW-0761 infusion. The reduction lasted for at least 4 months after the eighth infusion (Appendix Figs A2A, A2B; online only). The numbers of CD4+ CCR4−, and CD4− CD8+ cells in patients with untreated ATL were significantly lower than those in the controls. KW-0761 treatment led to a transient further reduction of those cells; however, recovery took place by the fifth infusion (Appendix Figs A2C, A2D; online only).

DISCUSSION

In the present multicenter phase II study, KW-0761 monotherapy demonstrated significant responses in patients with relapsed ATL with an acceptable toxicity profile. An ORR of 50% and median PFS and OS values of 5.2 and 13.7 months, respectively, were observed. Because the lower limit for an ORR with a 95% CI was 30%, this study met the primary end point. These results suggest an improvement over what has been achieved with other agents in relapsed ATL.[15] Cladribine was associated with an ORR of 7% (one of 15 patients),[16] and irinotecan hydrochloride treatment had an ORR of 38% (five of 13 patients) with a median duration of response of 31 days.[17] Antiviral therapy consisting of a combination of zidovudine and interferon, which has been proposed as a standard first-line therapy in leukemic subtypes of ATL,[18] was initially reported as having a median OS of 3.0 months in 19 patients with acute or lymphoma type ATL.[19] In addition, White et al[20] reported three objective responses lasting longer than 1 month with zidovudine plus interferon in 18 patients with ATL, of whom 15 had received prior therapy. Those observations collectively suggest that KW-0761 may offer an advantage over or provide an additional therapeutic option to the currently available therapy for relapsed ATL, although there were no direct comparisons.

On examining the results of ATL treatment according to disease site, disease in blood seemed to be more sensitive to KW-0761 than at other disease sites. Currently, we are unable to fully explain this difference; however, factors such as the KW-0761 delivery or the amount of ADCC effector cells such as natural killer (NK) cells and monocytes/macrophages in each disease site may be important.

Pharmacokinetic analyses demonstrated that the $t_{1/2}$ after the eighth administration of KW-0761 was nearly the same as that of circulating endogenous human IgG1, indicating good stability of this antibody in vivo. In addition, no anti-KW-0761 antibody was detected, suggesting that the antigenicity of this novel defucosylated mAb is not likely to be a problem clinically, consistent with findings in our preceding phase I study.[14]

The infusion reactions observed in the present study may also provide novel insights into problems associated with antibody therapy. It is generally recognized that complement plays a major role in infusion reactions,[21] but this mechanism cannot apply to KW-0761, because the agent is unable to mediate complement-dependent cytotoxicity.[11] Therefore, the infusion reactions observed here may have a different mechanism compared with those of other antibody therapies, such as rituximab. KW-0761 has a defucosylated Fc region, which markedly enhances ADCC because of increased binding affinity to the

Fcγ receptor on effector cells. Defucosylated IgG1 is a more potent activator of NK cells than nondefucosylated IgG1 during ADCC.[22] We surmise that the infusion reactions to KW-0761 were mainly induced by cytokines and related cytotoxic molecules released from highly activated NK cells.

The present study demonstrated that compared with the levels in the controls, KW-0761 led to a significant and lasting decrease in the number of CD4+ CCR4+ but not CD4+ CCR4− or CD4− CD8+ cells in patients with ATL. Consistent with the fact that CCR4 is expressed not only on T-helper type 2 cells but also on regulatory T (Treg) cells,[23-26] KW-0761 treatment also resulted in a significant and lasting decrease in CD4+ CD25+ FOXP3+ cells, including both ATL cells and endogenous non-ATL Treg cells.[27-29] Reduction or suppression of Treg cells is expected to be a potentially promising strategy for boosting antitumor immunity in patients with cancer, as observed in studies with ipilimumab,[30-33] although ipilimumab and KW-0761 have different targets; the former suppresses Treg cell function, and the latter decreases their number. Hence, KW-0761 could also lead to activation of antitumor immunity, which might also contribute to its potent anti-ATL response. Because ipilimumab causes immune-related AEs such as diarrhea and colitis, we were especially vigilant in monitoring for this type of AE. Because CCR4 contributes to lymphocyte skin-specific homing,[34] it was not surprising that skin rashes, which could be an immune-related AE, were frequently observed in the present KW-0761 study. Skin rashes, including the most severe case of Stevens-Johnson syndrome, the causal association of which with concomitant medications other than KW-0761 could not be excluded, proved to be manageable, and patients improved in all cases, although some needed systemic or topical steroid treatment. The observed better responses to KW-0761 in patients with grade 2 or higher skin rashes were highly impressive. However, the underlying mechanisms for this finding are not clear; thus, further detailed investigation is warranted. All of the 14 patients who developed grade 2 or higher skin rashes received five or more KW-0761 infusions according to the protocol, whereas only three of the 12 patients who developed no or grade 1 skin rashes received five or more KW-0761 infusions. This suggests the possibility that skin rashes were associated with the number of KW-0761 infusions. The Cochran-Mantel-Haenszel test stratified by the number of KW-0761 infusions ($\leq$ four v $\geq$ five) indicated a significant association between clinical response and skin rashes (no or grade 1 v grades 2 to 4; $P = .009$). However, the sample size is insufficient to draw such a conclusion.

Following on a phase III study (JCOG9801 [Japan Clinical Oncology Group 9801]) for untreated aggressive ATL,[5] the present promising results for KW-0761 monotherapy prompted us to conduct a subsequent randomized trial of VCAP-AMP-VECP chemotherapy with or without KW-0761 for previously untreated ATL (Clinicaltrials.gov: NCT01173887). CCR4 is also expressed on tumor cells from a subgroup of PTCL other than ATL, which also has an unfavorable prognosis.[2,35,36] Thus, we are currently conducting a phase II study of KW-0761 monotherapy for relapsed CCR4-positive PTCL (Clinicaltrials.gov:NCT01192984). In addition, Duvic et al[37] recently reported a phase I/II study of KW-0761 for refractory cutaneous T-cell lymphoma. They found that KW-0761 was well tolerated at doses of 0.1 to 1.0 mg/kg, and a promising ORR of 39% (15 of 38 patients) was achieved, although expression of CCR4 on lymphoma cells was not included as one of the eligibility criteria (Clinicaltrials.gov: NCT00888927). Furthermore, clinical trials of KW-0761 for patients with Hodgkin's lymphoma may be worth trying, because it has been reported that Hodgkin's lymphoma tumor cells produce CCR4 ligand molecules, and migratory CCR4-expressing Treg cells prevent a host immune attack on tumor cells, thereby creating an immunologically favorable environment for the tumor cells.[38]

Although this phase II study offers a novel promising treatment option (KW-0761) for patients with relapsed ATL, some limitations should be discussed. First, the present phase II study was relatively small, with consequent limitations on drawing definitive conclusions about the efficacy and safety profile of KW-0761. Second, patients received different prior systemic chemotherapy regimens, which could affect the results of the present study. Finally, the enrolled patients all had aggressive ATL, but three clinical subtypes (acute, lymphoma, and unfavorable chronic type) were included. Although there may be no significant differences in susceptibility to conventional chemotherapies between these subtypes, the heterogeneity of the enrolled patients might have affected the results.

In conclusion, this multicenter phase II study demonstrated that KW-0761 monotherapy showed clinically meaningful antitumor activity in patients with relapsed ATL, with an acceptable toxicity profile. Further investigation of KW-0761 for ATL and other T-cell neoplasms is warranted on the basis of the present results.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: Shiro Akinaga, Kyowa Hakko Kirin (C) **Consultant or Advisory Role:** Michinori Ogura, Kyowa Hakko Kirin (C) **Stock Ownership:** None **Honoraria:** Takashi Ishida, Kyowa Hakko Kirin **Research Funding:** Takashi Ishida, Kyowa Hakko Kirin **Expert Testimony:** None **Other Remuneration:** None

AUTHOR CONTRIBUTIONS

Conception and design: Takashi Ishida, Naokuni Uike, Kazuhito Yamamoto, Atae Utsunomiya, Kunihiro Tsukasaki, Shiro Akinaga, Masao Tomonaga, Kensei Tobinai, Ryuzo Ueda
Financial support: Shiro Akinaga
Provision of study materials or patients: Takashi Ishida, Tatsuro Joh, Naokuni Uike, Kazuhito Yamamoto, Atae Utsunomiya, Shinichiro Yoshida, Yoshio Saburi, Toshihiro Miyamoto, Shigeki Takemoto, Hitoshi Suzushima, Kunihiro Tsukasaki, Kisato Nosaka, Hiroshi Fujiwara
Collection and assembly of data: Takashi Ishida, Tatsuro Joh, Naokuni Uike, Kazuhito Yamamoto, Atae Utsunomiya, Shinichiro Yoshida, Yoshio Saburi, Toshishiro Miyamoto, Shigeki Takemoto, Hitoshi Suzushima, Kunihiro Tsukasaki, Kisato Nosaka, Hiroshi Fujiwara, Kensei Tobinai
Data analysis and interpretation: Kenji Ishitsuka, Hiroshi Inagaki, Michinori Ogura, Kensei Tobinai
Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. Shimoyama M: Diagnostic criteria and classification of clinical subtypes of adult T-cell leukaemia-lymphoma: A report from the Lymphoma Study Group (1984-87). Br J Haematol 79:428-437, 1991
2. Vose J, Armitage J, Weisenburger D: International peripheral T-cell and natural killer/T-cell lymphoma study: Pathology findings and clinical outcomes. J Clin Oncol 26:4124-4130, 2008
3. Uchiyama T, Yodoi J, Sagawa K, et al: Adult T-cell leukemia: Clinical and hematologic features of 16 cases. Blood 50:481-492, 1977
4. Tsukasaki K, Hermine O, Bazarbachi A, et al: Definition, prognostic factors, treatment, and response criteria of adult T-cell leukemia-lymphoma: A proposal from an international consensus meeting. J Clin Oncol 27:453-459, 2009
5. Tsukasaki K, Utsunomiya A, Fukuda H, et al: VCAP-AMP-VECP compared with biweekly CHOP for adult T-cell leukemia-lymphoma: Japan Clinical Oncology Group Study JCOG9801. J Clin Oncol 25:5458-5464, 2007
6. Utsunomiya A, Miyazaki Y, Takatsuka Y, et al: Improved outcome of adult T cell leukemia/lymphoma with allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant 27:15-20, 2001
7. Hishizawa M, Kanda J, Utsunomiya A, et al: Transplantation of allogeneic hematopoietic stem cells for adult T-cell leukemia: A nationwide retrospective study. Blood 116:1369-1376, 2010
8. Ishida T, Utsunomiya A, Iida S, et al: Clinical significance of CCR4 expression in adult T-cell leukemia/lymphoma: Its close association with skin involvement and unfavorable outcome. Clin Cancer Res 9:3625-3634, 2003
9. Yoshie O, Fujisawa R, Nakayama T, et al: Frequent expression of CCR4 in adult T-cell leukemia and human T-cell leukemia virus type 1-transformed T cells. Blood 99:1505-1511, 2002
10. Shinkawa T, Nakamura K, Yamane N, et al: The absence of fucose but not the presence of galactose or bisecting N-acetylglucosamine of human IgG1 complex-type oligosaccharides shows the critical role of enhancing antibody-dependent cellular cytotoxicity. J Biol Chem 278:3466-3473, 2003
11. Ishii T, Ishida T, Utsunomiya A, et al: Defucosylated humanized anti-CCR4 monoclonal antibody KW-0761 as a novel immunotherapeutic agent for adult T-cell leukemia/lymphoma. Clin Cancer Res 16:1520-1531, 2010
12. Ishida T, Iida S, Akatsuka Y, et al: The CC chemokine receptor 4 as a novel specific molecular target for immunotherapy in adult T-cell leukemia/lymphoma. Clin Cancer Res 10:7529-7539, 2004
13. Ito A, Ishida T, Utsunomiya A, et al: Defucosylated anti-CCR4 monoclonal antibody exerts potent ADCC against primary ATLL cells mediated by autologous human immune cells in NOD/Shi-scid, IL-2R gamma(null) mice in vivo. J Immunol 183: 4782-4791, 2009
14. Yamamoto K, Utsunomiya A, Tobinai K, et al: Phase I study of KW-0761, a defucosylated humanized anti-CCR4 antibody, in relapsed patients with adult T-cell leukemia-lymphoma and peripheral T-cell lymphoma. J Clin Oncol 28:1591-1598, 2010
15. Tobinai K: Current management of adult T-cell leukemia/lymphoma. Oncology (Williston Park) 14: 1250-1256, 2009
16. Tobinai K, Uike N, Saburi Y, et al: Phase II study of cladribine (2-chlorodeoxyadenosine) in relapsed or refractory adult T-cell leukemia-lymphoma. Int J Hematol 77:512-517, 2003
17. Tsuda H, Takatsuki K, Ohno R, et al: Treatment of adult T-cell leukaemia-lymphoma with irinotecan hydrochloride (CPT-11): CPT-11 Study Group on Hematological Malignancy. Br J Cancer 70:771-774, 1994
18. Bazarbachi A, Plumelle Y, Carlos Ramos J, et al: Meta-analysis on the use of zidovudine and interferon-alfa in adult T-cell leukemia/lymphoma showing improved survival in the leukemic subtypes. J Clin Oncol 28:4177-4183, 2010
19. Gill PS, Harrington W Jr, Kaplan MH, et al: Treatment of adult T-cell leukemia-lymphoma with a combination of interferon alfa and zidovudine. N Engl J Med 332:1744-1748, 1995
20. White JD, Wharfe G, Stewart DM, et al: The combination of zidovudine and interferon alpha-2B in the treatment of adult T-cell leukemia/lymphoma. Leuk Lymphoma 40:287-294, 2001
21. van der Kolk LE, Grillo-López AJ, Baars JW, et al: Complement activation plays a key role in the side-effects of rituximab treatment. Br J Haematol 115:807-811, 2001
22. Niwa R, Sakurada M, Kobayashi Y, et al: Enhanced natural killer cell binding and activation by low-fucose IgG1 antibody results in potent antibody-dependent cellular cytotoxicity induction at lower antigen density. Clin Cancer Res 11:2327-2336, 2005
23. Imai T, Nagira M, Takagi S, et al: Selective recruitment of CCR4-bearing Th2 cells toward antigen-presenting cells by the CC chemokines thymus and activation-regulated chemokine and macrophage-derived chemokine. Int Immunol 11: 81-88, 1999
24. Iellem A, Mariani M, Lang R, et al: Unique chemotactic response profile and specific expression of chemokine receptors CCR4 and CCR8 by CD4(+)CD25(+) regulatory T cells. J Exp Med 194: 847-853, 2001
25. Yagi H, Nomura T, Nakamura K, et al: Crucial role of FOXP3 in the development and function of human CD25+CD4+ regulatory T cells. Int Immunol 16:1643-1656, 2004
26. Ishida T, Ueda R: CCR4 as a novel molecular target for immunotherapy of cancer. Cancer Sci 97:1139-1146, 2006
27. Ishida T, Ueda R: Immunopathogenesis of lymphoma: Focus on CCR4. Cancer Sci 102:44-50, 2011
28. Karube K, Ohshima K, Tsuchiya T, et al: Expression of FoxP3, a key molecule in CD4CD25 regulatory T cells, in adult T-cell leukaemia/lymphoma cells. Br J Hematol 126:81-84, 2004
29. Yano H, Ishida T, Inagaki A, et al: Regulatory T-cell function of adult T-cell leukemia/lymphoma cells. Int J Cancer 120:2052-2057, 2007
30. Hodi FS, O'Day SJ, McDermott DF, et al: Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 363:711-723, 2010
31. Takahashi T, Tagami T, Yamazaki S, et al: Immunologic self-tolerance maintained by $CD25^{+}CD4^{+}$ regulatory T cells constitutively expressing cytotoxic T lymphocyte-associated antigen 4. J Exp Med 192:303-310, 2000
32. Zou W: Regulatory T cells, tumour immunity and immunotherapy. Nat Rev Immunol 6:295-307, 2006
33. O'Day SJ, Hamid O, Urba WJ: Targeting cytotoxic T-lymphocyte antigen-4 (CTLA-4): A novel strategy for the treatment of melanoma and other malignancies. Cancer 110:2614-2627, 2007
34. Campbell JJ, Haraldsen G, Pan J, et al: The chemokine receptor CCR4 in vascular recognition by cutaneous but not intestinal memory T cells. Nature 400:776-780, 1999
35. Ishida T, Inagaki H, Utsunomiya A, et al: CXCR3 and CCR4 expression in T-cell and NK-cell lymphomas with special reference to clinicopathological significance for peripheral T-cell lymphoma, unspecified. Clin Cancer Res 10:5494-5500, 2004
36. Weisenburger DD, Savage KJ, Harris NL, et al: Peripheral T-cell lymphoma, not otherwise specified: A report of 340 cases from the International Peripheral T-cell Lymphoma Project. Blood 117: 3402-3408, 2011
37. Duvic M, Pinter-Brown L, Foss FM, et al: Results of a phase 1/2 study for KW-0761, a monoclonal antibody directed against CC chemokine receptor type 4 (CCR4), in CTCL patients. Blood 116, 2010 (abstr 962)
38. Ishida T, Ishii T, Inagaki A, et al: Specific recruitment of CC chemokine receptor 4-positive regulatory T cells in Hodgkin lymphoma fosters immune privilege. Cancer Res 66:5716-5722, 2006

Ann Hematol (2012) 91:383–390
DOI 10.1007/s00277-011-1306-0

ORIGINAL ARTICLE

Retrospective analysis of primary gastric diffuse large B cell lymphoma in the rituximab era: a multicenter study of 95 patients in Japan

Tsutomu Tanaka · Kazuyuki Shimada · Kazuhito Yamamoto · Yoshiki Hirooka · Yasumasa Niwa · Isamu Sugiura · Kunio Kitamura · Hiroshi Kosugi · Tomohiro Kinoshita · Hidemi Goto · Shigeo Nakamura

Received: 18 February 2011 / Accepted: 26 July 2011 / Published online: 6 August 2011

Abstract Primary gastric diffuse large B cell lymphoma (PG-DLBCL) is common subtype of extranodal non-Hodgkin lymphoma. The optimal treatment strategy for PG-DLBCL in the rituximab era still remains unknown. To evaluate clinical outcomes of PG-DLBCL in the rituximab era, we conducted a retrospective, multicenter analysis of 95 patients with PG-DLBCL. In 58 patients with localized disease, 3-year progression-free survival (PFS) and overall survival (OS) were 91% and 91% for patients with six cycles of rituximab plus CHOP (R-CHOP) and 92% and 95% for patients with three to four cycles of R-CHOP plus radiotherapy (Log-rank test, P=0.595 and P=0.278, respectively). In 37 patients with advanced disease, 3-year PFS and 3-year OS were 43% and 64% for patients with R-CHOP chemotherapy with or without radiotherapy. On multivariate analysis, advanced stage and elevated serum LDH levels were independent predictors of survival in patients with PG-DLBCL. One patient with localized disease relapsed in lymph node, and eight patients with advanced disease relapsed in lymph node (n=3), stomach (n=2), central nervous system (CNS; n=2), and duodenum (n=1). Intriguingly, CNS relapse developed within 6 months after initial series of treatment (4.9 and 5.8 months, respectively), and stomach relapse developed in later phase (27.2 and 32.9 months, respectively). Clinical outcomes of PG-DLBCL were extremely favorable for localized-stage patients in the rituximab era, although these might be poor for advanced-stage patients even in the rituximab era. Further prospective analyses are warranted.

T. Tanaka (✉) · Y. Hirooka · H. Goto
Department of Gastroenterology,
Nagoya University Graduate School of Medicine,
65 Tsuruma-cho, Showa-ku,
Nagoya 466-8550, Japan
e-mail: tstanaka@med.nagoya-u.ac.jp

T. Tanaka · S. Nakamura
Department of Pathology and Clinical Laboratories,
Nagoya University Hospital,
Nagoya, Japan

K. Shimada · T. Kinoshita
Department of Hematology and Oncology,
Nagoya University Graduate School of Medicine,
Nagoya, Japan

K. Yamamoto
Department of Hematology and Cell Therapy,
Aichi Cancer Center,
Nagoya, Japan

Y. Niwa
Department of Endoscopy, Aichi Cancer Center,
Nagoya, Japan

I. Sugiura
Department of Hematology, Toyohashi Municipal Hospital,
Toyohashi, Japan

K. Kitamura
Department of Hematology, Ichinomiya Municipal Hospital,
Ichinomiya, Japan

H. Kosugi
Department of Hematology, Ogaki Municipal Hospital,
Ogaki, Japan

Keywords Primary gastric lymphoma · Diffuse large B cell lymphoma · Rituximab · Radiotherapy · Relapse

Introduction

Primary gastric diffuse large B cell lymphoma (PG-DLBCL) is the most common histologic type of extranodal non-Hodgkin lymphoma [1]. Regarding initial treatment for this condition, various modalities have long been used, including surgery, chemotherapy, and radiotherapy, either alone or in combination [2]. In a randomized controlled trial in patients with localized-stage PG-DLBCL, chemotherapy alone had a 90% cure rate, and 10-year overall survival was equivalent to that of surgery plus chemotherapy [3] while, in a subsequent prospective study in patients with localized-stage PG-DLBCL, chemotherapy followed by radiotherapy was shown to be highly effective [4]. These results lead to the replacement of surgical resection with more stomach-preserving therapy and chemotherapy followed by radiotherapy is commonly used treatment in localized disease. Nevertheless, it remains unclear whether optimal treatment is provided by chemotherapy alone or chemotherapy followed by radiotherapy [5].

With regard to advanced-stage PG-DLBCL, a prospective study by the *Groupe d'Etude des Lymphomes de l'Adult* (GELA) showed that gastrointestinal lymphomas behaved similarly to nodal lymphomas in patients treated with chemotherapy alone [6]. Since the appearance of this study, patients with advanced-stage PG-DLBCL have been mainly treated with chemotherapy alone because of the effectiveness and feasibility [1, 7].

The advent of rituximab, a chimeric anti-CD20 monoclonal antibody, has changed clinical treatment for DLBCL. A number of randomized clinical trials, conducted mainly for advanced-stage DLBCL, have shown that the addition of rituximab to cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) chemotherapy provides superior survival to CHOP chemotherapy alone [8, 9], and this combination has achieved consensus as the standard treatment especially in patients with advanced-stage DLBCL.

In PG-DLBCL, prospective analyses have been reported mainly in patients with localized disease treated with rituximab plus CHOP (R-CHOP) chemotherapy [10, 11]. However, the role of R-CHOP chemotherapy followed by radiotherapy in localized disease has not yet been evaluated. On the other hand, in advanced disease, there has been no detailed data in patients treated with R-CHOP chemotherapy even retrospective series. Here, we retrospectively analyzed a cohort of 95 patients with localized- and advanced-stage PG-DLBCL receiving R-CHOP chemotherapy with or without radiotherapy.

Methods

Patients

We conducted a retrospective analysis of 95 patients who were newly diagnosed with PG-DLBCL from January 1995 to January 2009 at Nagoya University Hospital and seven associated hospitals. PG-DLBCL was diagnosed if lesions were predominantly in the stomach when the expansion of disease is checked in full body at initial diagnosis [12]. Clinical stage was evaluated according to the Lugano staging system for gastrointestinal non-Hodgkin's lymphoma [13], in which stages I and II1 are categorized as localized disease, and II2, IIE, and IV as advanced disease [13]. All patients received staging investigations, including physical examination, laboratory data analysis, computed tomography (CT) of the chest and abdomen, gallium scintigraphy, or fluorine-18-fluorodeoxyglucose positron emission tomography, bone marrow aspiration/biopsy, and gastrofiberscopy (GF) with biopsy. Evaluation of central nervous system (CNS) involvement was by either or both computed tomography/magnetic resonance imaging and lumber puncture with cerebrospinal fluid analysis where indicated. The following clinical and laboratory data were available at the time of diagnosis: age; sex; performance status (PS); presence of B symptoms, bulky mass, bone marrow involvement, and CNS involvement; serum lactate dehydrogenase (LDH) level; clinical stage; and number of extranodal sites. For this study, International Prognostic Index (IPI) scores were determined, and the patients were categorized into low- (score 0–2) or high-risk groups (score 3–5) [14]. This study was approved by the institutional review board at each participating hospital and complied with all provisions of the Declaration of Helsinki.

Pathological studies

Histological sections were reviewed, and diagnosis was confirmed as DLBCL according to the fourth edition of the World Health Organization Classification of Tumors of Hematopoietic and Lymphoid Tissues [15]. The review was performed by two pathologists (S.N. and T.T.) at the Department of Pathology and Clinical Laboratories, Nagoya University Hospital. Immunohistochemical staining and scoring for CD10, BCL-6, and MUM-1/IRF4 were performed on formalin-fixed paraffin-embedded tissues from patients diagnosed with PG-DLBCL and scored as positive if 30% or more of tumor cells were labeled [16]. The patients were then assigned as germinal center B cell-like (GCB) phenotype or non-GCB phenotype using the algorithm of Hans et al. [16].

Treatment

Analysis was restricted to patients who received CHOP chemotherapy (CHOP or CHOP-like regimen) plus rituximab (R-CHOP) or R-CHOP chemotherapy followed by radiotherapy as initial therapy. Rituximab dosage for all patients was 375 mg/m^2. Therapeutic strategies were determined by the attending physician in each hospital. Regarding localized-stage PG-DLBCL, selection of R-CHOP chemotherapy alone, or R-CHOP chemotherapy followed by radiotherapy was not decided in advance of diagnosis.

Response to treatment

Complete response (CR) was defined as the disappearance of all clinical evidence of disease, negative gastric biopsy, and recovery of all laboratory and radiological abnormalities related to the disease. Partial response (PR) was indicated by a decrease of more than 50% in the sum of the products of the maximum perpendicular diameters of each measurable lesion. Progressive disease (PD) was indicated by at least a 25% increase in the size of any preexisting lesions or by the appearance of any new lesions during or after therapy. Stable disease was neither PR nor PD. Relapse disease (RD) was the appearance of any new lesion in patients who had achieved CR. Overall survival (OS) was defined as the time from initial diagnosis to the date of death from any cause or of last follow-up. PFS was defined as the duration from initial diagnosis to the date of progression, relapse, death from any cause, or last follow-up, whichever occurred first.

Gastrointestinal-specific toxicities

Gastrointestinal-specific toxicities such as gastric hemorrhage, gastric perforation, and gastric obstruction during initial treatment were evaluated. Gastric hemorrhage was defined as symptoms of melena or hematemesis and the presence of hemorrhage confirmed by GF; gastric obstruction as symptoms of vomiting, eating difficulty, and the presence of stenosis confirmed by GF; and gastric perforation as the presence of free air around the stomach in the abdominal cavity on CT.

Statistical analysis

Patient characteristics between treatment groups were compared with Fisher's exact test and median age with the Mann–Whitney *U* test. OS and PFS were assessed by the Kaplan–Meier method and compared between groups by the log-rank test. The impact of independent prognostic factors on OS was evaluated by univariate and multivariate analyses using a Cox proportional hazards model. Variable factors were as follows: sex; age; performance status; presence of B symptoms, bulky mass, and bone marrow involvement; expression of the GCB phenotype; number of extranodal sites; serum LDH level; addition of rituximab; and addition of radiotherapy. All *P* values were based on two-sided tests and *P* values less than 0.05 were considered significant. All statistical analyses were performed using the Statistical Software Package for the Social Sciences (SPSS version 11.0 for Windows; SPSS Inc., Chicago, IL).

Results

Patient characteristics

Patient characteristics are shown in Table 1. Of the 95 patients analyzed in this study, 50 were male and 45 were female with a median age of 68 years (range, 32–86 years). The proportion of GCB phenotype was lower compared with that of non-GCB type (42% and 58%, respectively). Seven variables showed a significant difference between localized- and advanced-stage groups, namely PS, number of extranodal sites, serum LDH level, IPI risk group, bulky mass, and radiotherapy. Frequent extranodal involvements other than the stomach were liver in four patients, spleen duodenum, and bone marrow in three patients and bone in two patients. *Helicobacter pylori* infection was found in 27 of 49 patients (55%) who could be examined for *H. pylori* status in PG-DLBCL. Eleven of 27 patients (41%) with *H. pylori*-positive PG-DLBCL received eradication therapy before or after initial chemotherapy. In 95 patients diagnosed with PG-DLBCL, eight patients (8%) had DLBCL with marginal-zone lymphoma of mucosa-associated lymphoid tissue (MALT) component. *H. pylori* status was recognized in four of six patients (67%) with DLBCL in the presence of MALT component and not examined in two patients. In eight patients of DLBCL with MALT component, all patients were classified into non-GCB phenotype on the immunohistochemical staining.

Treatment

Of the 58 patients with localized disease, 35 patients (60%) received a median of three courses (range, three to four) of R-CHOP chemotherapy followed by radiotherapy, while the remaining 23 (40%) received a median of six courses (range, two to eight) of R-CHOP chemotherapy without radiotherapy. Of the 37 patients with advanced disease, 35 patients (95%) received R-CHOP chemotherapy alone and CHOP (n=35) or CHOP-like regimen (n=2) combined with rituximab. Two patients (5%) received three cycles of R-CHOP chemotherapy combined with radiotherapy.

Table 1 Patient characteristics

Variable	Total (N=95) N (%)	Localized stage (n=58) n (%)	Advanced stage (n=37) n (%)	P value*
Age				
Median age	68	68	67	0.722
Range	32–86	32–84	35–86	
Sex				
Male	50 (52)	30 (51)	20 (54)	0.824
Female	45 (48)	28 (49)	17 (46)	
Performance status				
0–1	89 (94)	57 (98)	31 (84)	0.013
2–4	6 (6)	1 (2)	6 (16)	
Lugano stage				
I	33 (35)	33 (57)	–	
II1	25 (26)	25 (43)	–	
II2	10 (11)	–	10 (27)	
IIE	4 (4)	–	4 (11)	
IV	23 (24)	–	23 (62)	
Extranodal sites				
Fewer than 2 (stomach only)	81 (85)	58 (100)	23 (62)	<0.0001
2 or more	14 (15)	0	14 (38)	
Serum LDH level				
Elevated	29 (31)	9 (15)	20 (54)	0.0002
IPI score				
<3	75 (79)	57 (98)	18 (49)	<0.0001
≥3	20 (21)	1 (2)	19 (51)	
B symptom present	19 (20)	10 (17)	9 (24)	0.438
Bulky mass present	9 (9)	1 (2)	8 (22)	0.002
Bone marrow involvement	3 (3)	0	3 (8)	0.056
Treatment				
Six cycles of R-CHOP	58 (61)	23 (39)	35 (95)	<0.0001
Three to four cycles of R-CHOP +Radiotherapy	37 (39)	35 (61)	2 (5)	
ASCT				
Yes	1 (1)	0	1 (3)	0.389
No	94 (99)	58	36 (97)	
Hans' algorism				
GCB phenotype	40 (42)	22 (37)	18 (49)	0.302
Non-GCB phenotype	45 (58)	36 (63)	19 (51)	

Abbreviations: *LDH* lactate dehydrogenase, *ASCT* autologous stem cell transplantation, *GCB* germinal center B cell-like

*P values are for the comparison of localized- and advanced-stage group

Efficacy

Localized-stage patient

Of the 58 patients with localized disease, 51 patients (88%) and seven patients (12%) achieved CR and PR. No patient developed PD. With a median follow-up for surviving patients of 34.5 months (range, 4.9–89.3 months), 3-year PFS and OS were 93%. With regard to radiotherapy, CR rate in the localized disease was 83% and 91% in six cycles of R-CHOP and in three to four cycles of R-CHOP plus radiotherapy, respectively. 3-Year PFS and OS were 91% and 91% in patients with six cycles of R-CHOP and 92% and 95% in those with three to four cycles of R-CHOP plus radiotherapy (Log-rank test, P=0.595 and P=0.278, respectively; Fig. 1a, b). Twenty-two patients (38%) were classified as the GCB phenotype and 36 (62%) as the non-GCB phenotype. No significant difference in 3-year OS was seen between the GCB and non-GCB phenotypes (92% vs 96%; P=0.886).

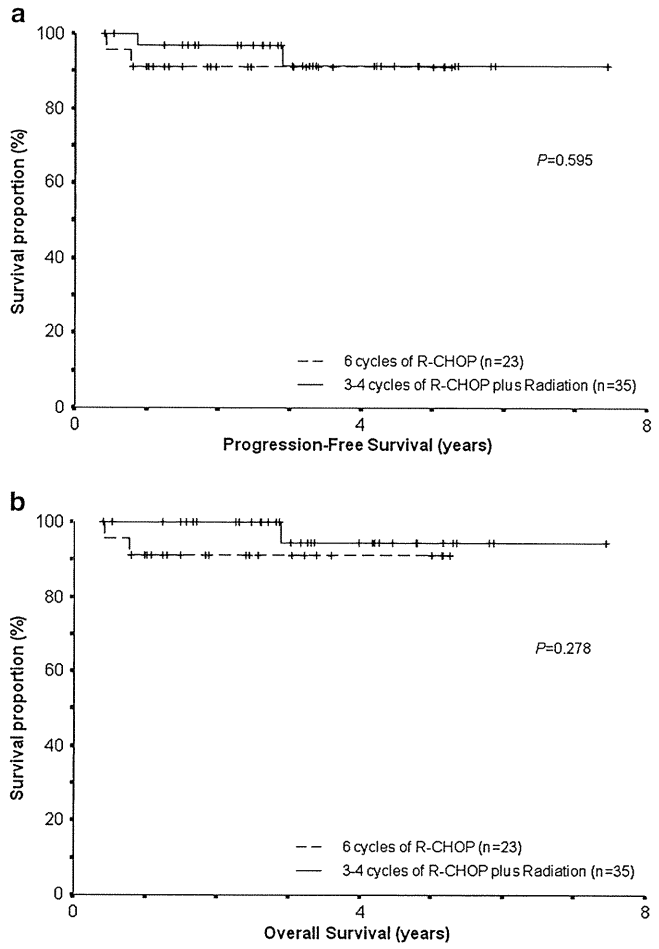

Fig. 1 **a** Progression-free and **b** overall survival of 58 patients receiving six cycles of R-CHOP (n=23) and three to four cycles of R-CHOP plus radiotherapy (n=35) in localized disease

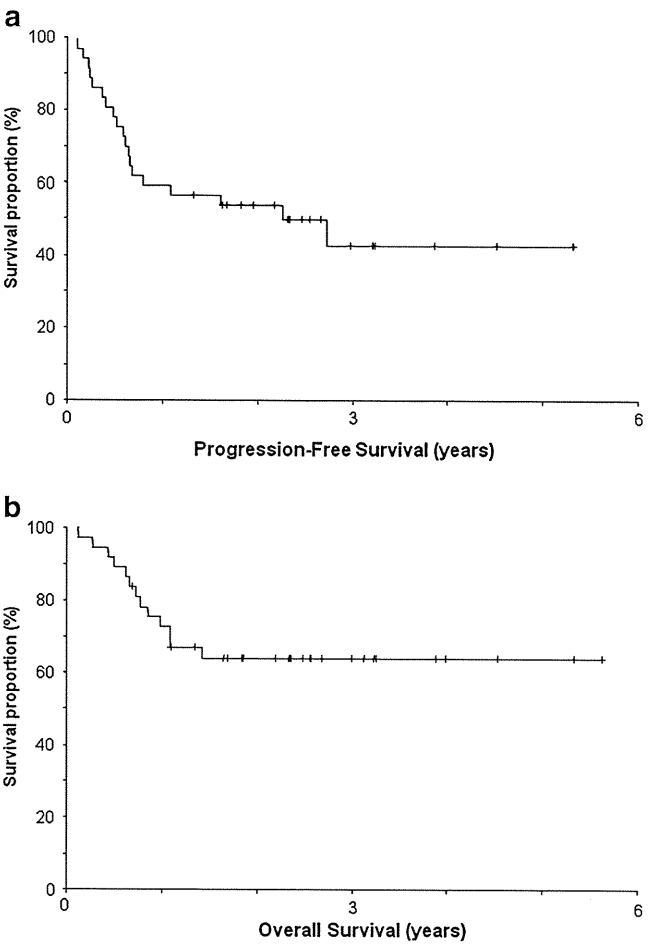

Fig. 2 **a** Progression-free and **b** overall survival of 37 patients receiving R-CHOP chemotherapy with or without radiotherapy in advanced disease

Advanced-stage patient

Of the 37 patients with advanced disease, 29 (78%) and two (5%) achieved CR and PR. Four patients (11%) developed PD. With a median follow-up for the surviving patients of 30.2 months (range, 8.2–67.5 months), 3-year PFS and OS were 43% and 64%, respectively (Fig. 2a, b). Eighteen patients (49%) were classified as the GCB phenotype and 19 (51%) as the non-GCB phenotype. No significant difference in 3-year OS was seen between the GCB and non-GCB phenotypes (58% vs 71%; P=0.303).

Toxicity

Surgical events such as gastric hemorrhage, gastric perforation, and gastric obstruction are shown in Table 2. Gastric perforation was not identified in any patient. Gastric hemorrhage occurred in one patient (1%) in the localized stage and two (5%) in the advanced stage, and gastric obstruction in two patients (3%) in the localized stage and four (5%) in the advanced stage. The frequency of gastric hemorrhage and gastric obstruction between the localized and advanced stage did not significantly differ (P=0.558 and P=0.999, respectively).

Relapsed disease

Localized-stage patient

Among the 51 patients achieving CR after initial treatment, only one patient (2%) developed RD in lymph node with 10.4 months of interval between initial diagnosis and relapse (Table 3).

Advanced-stage patient

Among 29 patients achieving CR, eight patients (28%) developed RD. Sites of relapse were lymph node (n=3), stomach (n=2), CNS (n=2), and duodenum (n=1). Median interval between initial diagnosis and relapse was 7.8 months (range, 4.9–32.9 months). In patients with RD in the CNS or stomach, median interval between initial

Table 2 The frequency of gastric perforation, hemorrhage, and obstruction

Variable	Localized stage (n=58)			Advanced stage (n=37)			
	Six cycles of R-CHOP (n=23)	Three to four cycles of R-CHOP+radiation (n=35)	Total	Six cycles of R-CHOP (n=35)	Three to four cycles of R-CHOP+radiation (n=2)	Total, N (%)	P value
Hemorrhage	0	1	1 (1)	2	0	2 (5)	0.558
Perforation	0	0	0	0	0	0	
Obstruction	1	1	2 (3)	2	0	2 (5)	0.999

diagnosis and relapse was 5.4 and 30.0 months, respectively (Table 3). Of the two patients relapsed in stomach, one was *H. pylori*-positive DLBCL with MALT component and achieved CR with six cycles of R-CHOP chemotherapy. Eradication therapy was not performed before or after chemotherapy. MALT lymphoma occurred in the same lesion of the stomach 27 months later. After eradication therapy, the relapsed lesion disappeared. The other who was *H. pylori*-negative DLBCL relapsed with DLBCL in different lesion of the stomach 32 months later.

Prognostic factors

All patients with localized and advanced disease were analyzed together. In univariate analysis, seven factors were associated with shorter survival, namely poor performance status, involvement of two or more extranodal sites, advanced stage, elevated serum LDH level, presence of bulky mass, presence of B symptoms, and presence of bone marrow involvement. The other three factors, namely sex, age, and expression of the GCB phenotype were not predictive of survival on univariate analysis. In addition, the GCB phenotype was not predictive of survival in both patients with localized and advanced group. Multivariate analysis identified advanced stage (hazard ratio (HR), 4.807; 95% confidence interval (CI), 1.075-21.739; P=0.039) and elevated serum LDH level as independent predictors of survival (HR, 4.901; 95% CI, 1.035–23.255; P=0.045; Table 4).

Discussion

We found that the clinical outcomes in patients with localized-stage PG-DLBCL were extremely favorable in the both groups treated with three cycles of R-CHOP plus radiotherapy and six cycles of R-CHOP, and those tended to be similar. Furthermore, the clinical outcome in patients with advanced-stage PG-DLBCL treated with R-CHOP chemotherapy might be poor. Although retrospective, these findings might be informative in patients with PG-DLBCL in the rituximab era.

In this study, patients with localized-stage PG-DLBCL treated with six cycles of R-CHOP had a CR rate of 83% and 3-year OS of 91%. There have been two reported studies that have prospectively evaluated PG-DLBCL mainly in localized-stage using R-CHOP chemotherapy alone as follows: Wohrer et al. reported a CR rate of 87% (13 of 15 patients) in patients treated with six cycles of R-CHOP [10]. Aviles et al. showed 5-year OS of 95% in 42 patients treated with six cycles of R-CHOP [11]. Although current study was retrospective, our

Table 3 Site of relapse in patients with a CR after initial therapy

Case no.	Age/sex	Stage	Lugano	LDH	IPI score	Extranodal involvement (excluding stomach)	Therapy	Course	Site of relapse	Time to relapse (months)
1	52/F	Localized	I	294	1		R-CHOP+Rad	3	Cervical LN	11.1
2	57/M	Advanced	II2	461	1		R-CHOP	8	CNS	5.8
3	53/M	Advanced	IIE	220	0	Duodenum	R-CHOP	8	Duodenum	8.0
4	71/M	Advanced	IV	398	3		R-CHOP	6	CNS	4.9
5	57/M	Advanced	IV	237	2	Spleen, liver	R-CHOP	7	Mediastinal LN	6.2
6	35/M	Advanced	IV	209	1		R-CHOP	6	Stomach	27.2
7	73/F	Advanced	IV	188	2		R-CHOP	8	Stomach	32.9
8	67/M	Advanced	IV	390	3		R-CHOP	8	Paraorta LN	7.6
9	69/F	Advanced	IV	434	4	Pancreas	R-CHOP	8	Paraorta LN	20.7

CNS central nervous system

Table 4 Univariate and multivariate analysis for OS in patients with PG-DLBCL

Variable	Subgroup	Univariate analysis Hazard ratio [95% CI]	*P* value	Multivariate analysis Hazard ratio [95% CI]	*P* value
Sex	Female vs. male	1.129 [0.420–3.039]	0.885	3.636 [0.952–13.888]	0.058
Age	<60 vs. ≥60	2.096 [0.596–7.352]	0.248	3.194 [0.605–16.949]	0.171
Performance status	0–1 vs. 2–4	5.917 [1.893–18.518]	0.002	2.028 [0.458–8.928]	0.351
Extranodal site	One vs. two or more	3.846 [1.386–10.638]	0.009	1.381 [0.104–7.209]	0.660
Lugano stage	Localized vs. advanced	8.064 [2.298–28.571]	0.001	4.807 [1.075–21.739]	0.039
Serum LDH level	Normal vs. high	6.535 [2.267–18.867]	0.0005	4.901 [1.035–23.255]	0.045
Bulky mass	No vs. yes	3.533 [1.137–10.989]	0.029	1.054 [0.252–4.418]	0.942
B symptom	No vs. yes	3.300 [1.125–8.849]	0.018	2.906 [0.822–10.309]	0.097
Bone marrow involvement	No vs. yes	6.250 [1.385–27.777]	0.017	1.738 [0.224–13.484]	0.596
GCB phenotype	GCB vs. non-GCB	1.293 [0.470–3.558]	0.618	1.769 [0.469–6.666]	0.398

CI confidence interval

result was comparable with previous prospective data in localized-stage PG-DLBCL.

Our analysis of all patients treated with rituximab-containing regimen showed that three to four cycles of R-CHOP plus radiotherapy tended to be similar to six cycles of R-CHOP in terms of PFS and OS. These results suggested that the optimal treatment strategy for localized-stage PG-DLBCL in the rituximab era, in other words, the relative merit of three cycles of R-CHOP followed by involved field radiation versus six cycles of R-CHOP thus remains uncertain. Our results support the use of six cycles of R-CHOP without involved field radiation as an important treatment option for localized-stage PG-DLBCL in the rituximab era.

With regard to advanced-stage PG-DLBCL, our study showed that 3-year OS was 64% with half proportion of high-risk group (IPI score ≥3). However, compared with previous study in patients with DLBCL treated with R-CHOP chemotherapy, 3-year OS was similar to patients with DLBCL in high-risk group [14]. In fact, 7 of 12 patients who developed PD or RD died within 1 year after PD or RD despite the use of salvage therapies, and five of eight patients who developed RD did not achieve CR despite salvage therapies. Considering this poor survival for advanced disease, another therapeutic strategy should be developed. In our case, one patient who received autologous stem cell transplantaion (ASCT) in the initial treatment survived without relapse at the end of the study. ASCT in the initial treatment might be worthy of evaluation as a treatment option for advanced patients especially with elevated LDH level as a poor prognostic factor.

We found two notable remarks in the site of relapse. First, relapse in the stomach was frequent, and *H. pylori* eradication therapy should be performed even if CR was obtained, especially in patients with DLBCL with MALT component. Second, CNS relapse was frequent when time to relapse was short (median, 5.4 months). Given previous findings that early relapse in the CNS within 6 months of initial therapy might have been due to subclinical CNS involvement at the time of diagnosis, however, this finding requires careful interpretation [17]. Of the two patients experiencing CNS relapse in the present study, neither of patients had undergone CNS evaluation at initial diagnosis, and the possibility of subclinical CNS involvement at the time of initial diagnosis could not be excluded.

Massive hemorrhage, gastric obstruction, or gastric perforations in patients with PG-DLBCL are surgical events related to chemotherapy and radiotherapy. In previous studies, the rate of these complications with chemotherapy with or without rituximab was 12% to 25% [18, 19]. In our study, however, the rate of surgical events was 7% with no gastric perforation, suggesting that the frequency of surgical complications was not high in the rituximab era.

Several limitations of our study warrant mention. First, this retrospective study might have been influenced by unrecognized bias. Second, the number of treatment courses was not standardized and thus treatment intensity varied. This variation in our present study, which was also present in previous clinical trials for localized DLBCL [9, 20], might have lead to the underestimation of effects.

In conclusion, we found the clinical outcome in patients with localized-stage PG-DLBCL treated with three cycles of R-CHOP plus radiotherapy tended to be similar to six cycles of R-CHOP with an extremely favorable effect. Furthermore, the clinical outcome in patients with advanced-stage PG-DLBCL might be poor even in the rituximab era. Further prospective analyses are warranted.

Acknowledgments We are indebted to Dr. Tatsuya Ito, Department of Hematology, Anjo Kosei Hospital, and Dr. Hisamitsu Suzuki, Department of Hematology, Okazaki Municipal Hospital, for their contribution to the collection of patient data.

Funding This work was supported in part by a Grant-in-aid for Cancer Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan, and a Grant-in-aid for delineation of molecular biological profile of the refractory lymphoid malignancy and the development of its tumor type-specific management from the Ministry of Health, Labor, and Welfare, Japan.

Conflict of interest disclosure The authors declare no competing financial interests.

References

1. Koch P, del Valle F, Berdel WE, et al. German Multicenter Study Group. Primary gastrointestinal non-Hodgkin's lymphoma: II. Combined surgical and conservative or conservative management only in localized gastric lymphoma—results of the prospective German Multicenter Study GIT NHL 01/92. J Clin Oncol. 2001;19:3874–83.
2. Brands F, Monig SP, Raab M (1997) Treatment and prognosis of gastric lymphoma. Eur J Surg 163:803–813, Review
3. Aviles A, Nambo MJ, Neri N et al (2004) The role of surgery in primary gastric lymphoma: results of a controlled clinical trial. Ann Surg 240:44–50
4. Ishikura S, Tobinai K, Ohtsu A et al (2005) Japanese multicenter phase II study of CHOP followed by radiotherapy in stage I-II, diffuse large B-cell lymphoma of the stomach. Cancer Sci 96:349–352
5. Martinelli G, Gigli F, Calabrese L et al (2009) Early stage gastric diffuse large B-cell lymphomas: results of a randomised trial comparing chemotherapy alone versus chemotherapy+involved field radiotherapy. (IELSG 4). Leuk Lymphoma 50:925–931
6. Salles G, Herbrecht R, Tilly H et al (1991) Aggressive primary gastrointestinal lymphomas: review of 91 patients treated with the LNH-84 regimen. A study of the Groupe d'Etude des Lymphomes Agressifs. Am J Med 90:77–84
7. Coiffier B, Salles G (1997) Does surgery belong to medical history for gastric lymphomas? Ann Oncol 8:419–421
8. Coiffier B, Lepage E, Briere J et al (2002) CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med 346:235–242
9. Pfreundschuh M, Trümper L, Osterborg A, MabThera International Trial Group et al (2006) CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. Lancet Oncol 7:379–391
10. Wöhrer S, Püspök A, Drach J et al (2004) Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) for treatment of early-stage gastric diffuse large B-cell lymphoma. Ann Oncol 15:1086–1090
11. Avilés A, Castañeda C, Cleto S et al (2009) Rituximab and chemotherapy in primary gastric lymphoma. Cancer Biother Radiopharm 24:25–28
12. Lewin KJ, Ranchod M, Dorfman RF (1978) Lymphomas of the gastrointestinal tract: a study of 117 cases presenting with gastrointestinal disease. Cancer 42:693–707
13. Rohatiner A, d'Amore F, Coiffier B et al (1994) Report on a workshop convened to discuss the pathological and staging classifications of gastrointestinal tract lymphoma. Ann Oncol 5:397–400
14. Sehn LH, Berry B, Chhanabhai M et al (2007) The revised International Prognostic Index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. Blood 109:1857–1861
15. Swerdlow SH, Campo E, Harris NL et al (2008) WHO classification of tumours of haematopoietic and lymphoid tissues, 4th edn. International Agency for Research on Cancer, Lyon
16. Hans CP, Weisenburger DD, Greiner TC et al (2004) Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. Blood 103:275–282
17. Bernstein SH, Unger JM, Leblanc M, Friedberg J, Miller TP, Fisher RI (2009) Natural history of CNS relapse in patients with aggressive non-Hodgkin's lymphoma: a 20-year follow-up analysis of SWOG 8516–the Southwest Oncology Group. J Clin Oncol 27:114–119
18. Huang J, Jiang W, Xu R et al (2010) Primary gastric non-Hodgkin's lymphoma in Chinese patients: clinical characteristics and prognostic factors. BMC Cancer 10:358
19. Spectre G, Libster D, Grisariu S et al (2006) Bleeding, obstruction, and perforation in a series of patients with aggressive gastric lymphoma treated with primary chemotherapy. Ann Surg Oncol 13:1372–1378
20. Persky DO, Unger JM, Spier CM et al (2008) Phase II study of rituximab plus three cycles of CHOP and involved-field radiotherapy for patients with limited-stage aggressive B-cell lymphoma: Southwest Oncology Group Study 0014. J Clin Oncol 26:2258–2263

Int J Hematol (2011) 93:502–508
DOI 10.1007/s12185-011-0822-y

ORIGINAL ARTICLE

High maximum standard uptake value (SUVmax) on PET scan is associated with shorter survival in patients with diffuse large B cell lymphoma

Dai Chihara · Yasuhiro Oki · Hiroshi Onoda · Hirofumi Taji · Kazuhito Yamamoto · Tsuneo Tamaki · Yasuo Morishima

Received: 4 January 2011 / Revised: 21 February 2011 / Accepted: 22 March 2011 / Published online: 6 April 2011

Abstract FDG-PET scan plays an important role in response assessment in diffuse large B cell lymphoma (DLBCL). In this study, we evaluated the prognostic value of maximum standard uptake (SUVmax) on pretreatment PET scan in DLBCL. Among 169 patients with DLBCL newly diagnosed and treated with R-CHOP between 2003 and 2008, 110 patients who had undergone pretreatment PET scan in single institute using an identical protocol were reviewed and analyzed. SUVmax at the predominant lesion on PET scan and other patient characteristics were evaluated for their association with complete response (CR) rate, overall survival (OS) and progression-free survival (PFS). The median SUVmax was 18.1 (2.0–36.4). There was no significant association between high SUV and other characteristics with the exception of PS $\geq$ 2 and Ki-67. Multivariate analysis revealed the independent association between high SUVmax and lower CR rate. The 3-year PFS rates in patients with SUV $<$ 30 and those with SUV $\geq$ 30 were 78 and 51%, respectively ($p = 0.06$). The 3-year OS rates were 86 and 71%, respectively ($p = 0.03$). Multivariate analysis revealed that high SUVmax is a significant poor prognostic factor for both PFS and OS, independent of IPI. We showed the important prognostic value of pretreatment SUVmax of PET scan in DLBCL.

Keywords Diffuse large B cell lymphoma · FDG-PET · Standard uptake value · Prognostic factor

1 Introduction

A large proportion of patients diagnosed with diffuse large B cell lymphoma (DLBCL) are cured with initial treatment with combination chemotherapy. The management of refractory and recurrent disease, however, remains challenging. One strategy to improve outcome is to select patients with poor prognostic features and to provide novel or more intensive treatment. Particularly, appropriate staging evaluation as well as precise response assessment is essential for determining optimal treatment modalities in patients with DLBCL, where 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) scan now has a major role.

FDG-PET measures the amount of metabolic activity at a site in the body using the gamma ray signals given off by the injected FDG. In DLBCL, the role of FDG-PET has been established best in response assessment after treatment, and has been incorporated in the revised International Workshop Criteria (IWG) [1, 2]. In addition, extensive studies have evaluated the value of early response assessment with FDG-PET during the course of chemotherapy in an attempt to identify the patient population with poor prognosis, and potentially to change treatment strategies in these patients [3]. FDG-PET is commonly performed also before treatment to identify the area of DLBCL involvement, but the actual role of pretreatment FDG-PET remains unclear [4, 5].

D. Chihara · Y. Oki (✉) · H. Onoda · H. Taji · K. Yamamoto · Y. Morishima
Department of Hematology and Cell Therapy, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan
e-mail: yooki-tky@umin.ac.jp

T. Tamaki
Department of Radiology, Nagoya PET Imaging Center, Aichi, Japan

Abnormal FDG uptake is measured by standard uptake value (SUV), and represented by mean, or more commonly, the maximum SUV (SUVmax), correlates with the cellular metabolism, which can be influenced by the cell cycle speed to some degree. In fact, several reports suggested the association between aggressiveness of lymphoma and SUV [6, 7].

The prognostic value of maximum SUV (SUVmax) at diagnosis has been evaluated in solid tumors, and these studies suggest that high SUVmax is associated with poor prognosis in esophageal cancer, head and neck cancer, and non-small cell lung cancer [8–12]. In addition, a small study of gastric lymphoma suggested a potential prognostic value of SUVmax on pretreatment FDG-PET [13]. And also, several recent studies of interim FDG-PET in DLBCL suggested a prognostic value of SUV-based assessment during the course of chemotherapy [14, 15]. In the present study, we retrospectively evaluated the prognostic value of SUVmax at the predominant lesion on pretreatment FDG-PET in 132 patients with DLBCL.

2 Materials and methods

2.1 Patients

We reviewed medical records of 169 patients with DLBCL newly diagnosed and treated with R-CHOP-based therapy at Aichi Cancer Center Hospital between April 2003 and December 2008. We selected 2003 as the genesis of study population because it is the year when R-CHOP became the standard of therapy for DLBCL and PET scan became a part of routine staging evaluation. Staging evaluation for newly diagnosed patients consisted of physical examination, systemic CT scan, FDG-PET scan, bone marrow aspiration and biopsy, upper gastrointestinal endoscopy. Pretreatment PET scan was not available in 37 patients for various reasons (e.g. steroid was given for symptom palliation before PET scan), and 22 patients underwent PET scan in other institution. Thus, a total of 110 patients were analyzed in this study. Multiple pretreatment patient characteristics were collected along with the SUVmax on PET (Table 1). Bulky disease was defined by the size greater than 7 cm. International Prognostic Index (IPI) was scored from 0 to 5 by age >60, stage 3/4, performance status (PS) ≥2, serum lactate dehydrogenase level (LDH) higher than upper limit of normal range and number of extranodal involvement ≥2. IPI risk groups were defined by score of 0–2 and 3–5, which correspond to low/low intermediate and high/high intermediate by classical IPI risk group [16], or very good/good and poor by revised IPI risk group, respectively [17]. DLBCL subtypes by immunophenotype [i.e. germinal center B cell type (GCB) and non-GCB] were defined as previously described [18]. These pretreatment characteristics, including SUVmax were evaluated for their association with CR rate, overall survival (OS) and progression-free survival (PFS, time from diagnosis to disease progression, relapse, or death of any cause). This study has been approved by the Institutional Review Board of the Aichi Cancer Center.

2.2 FDG-PET and SUVmax

All FDG-PET scans were performed by Discovery LS (GE Medical Systems, Waukesha, WI) with identical protocol. Patients were fasted for at least 6 h prior to the visit to the imaging center. A low-dose CT scan (120–140 kV, 100 mA) was first performed for attenuation correction and precise anatomic localization on PET scan. Patients received intravenous injection of 4.0 MBq/kg of 18FDG. After the injection, patients sit at rest until PET scan. The blood glucose level before injection was not routinely collected. The image of PET scan was acquired in 60 min following an intravenous injection from the level of the skull base to the upper thigh. The acquisition duration of emission images was 3-min per bed position. PET image acquisition was performed with 2D method and the image reconstruction was done with ordered subset expectation maximization method [19]. The PET images were interpreted by physicians, who were trained in nuclear medicine, and were unaware of the results of other imaging studies.

The SUVmax was collected from the predominant lesion, and was calculated based on the attenuation-corrected images, the amount of injected 18F-FDG, and the body weight (SUV = [decay corrected activity (kBq)/tissue volume (ml)]/[injected FDG activity (kBq)/body weight (g)]).

2.3 Statistical analysis

Fisher's exact tests were used for the descriptive statistical analyses on categorical data. OS and PFS were calculated using Kaplan–Meier method, and were compared between two groups by log-rank test. Logistic regression models were used to evaluate the association between multiple characteristics and complete response (CR). Patient characteristics were analyzed for their association with OS and PFS using Cox proportional hazard models. In these models, characteristics with $p < 0.10$ in the univariate analyses were included in the multivariate analyses, and a backward elimination with a p cutoff of 0.05 was used. In the final models of the multivariate analyses, any parameter could be put back into the model if the final $p < 0.05$. In the multivariate analyses, IPI was incorporated in the model, but not each of the IPI determinants, unless IPI was

Table 1 Patient characteristics

Parameters	SUVmax <30 (*N*)	SUVmax ≥30 (*N*)	*p*
All	94	16	
Age (years)			
≤60	38	6	0.13
>60	56	10	
Sex			
Male	49	12	0.11
Female	45	4	
Stage			
1/2	58	7	0.27
3/4	36	9	
PS			
0/1	84	10	0.01
≥2	10	6	
LDH			
Normal	54	8	0.60
High	40	8	
Number of extranodal involvement			
0/1	74	15	0.30
≥2	20	1	
Bone marrow involvement			
Absent	88	15	1.00
Present	6	1	
B symptoms			
Absent	81	12	0.27
Present	13	4	
Bulky disease (>7 cm)			
Absent	67	11	1.00
Present	27	5	
IPI risk group			
Low	48	5	0.46
Low intermediate	18	5	
High intermediate	18	4	
High	10	2	
Serum albumin			
Lower than LLN	21	6	0.22
Normal	71	10	
sIL2R (U/mL)			
<1,000	48	7	0.79
≥1,000	46	9	
Absolute lymphocyte count			
$<1.0 \times 10^9$/L	40	7	1.00
$\geq 1.0 \times 10^9$/L	53	9	
β2-microgloburin (mg/L)			
<2	41	5	0.73
≥2	25	4	
Immunophenotype			
GCB	28	5	1.00
Non-GCB	40	7	
Bcl-2			
Positive	56	9	1.00
Negative	29	5	
Ki-67			
Median (range)%	70 (20–100)	90 (90–90)	0.08
Initial treatment			
R-CHOP + RT	43	5	0.41
R-CHOP	51	11	
ASCT			
As a primary treatment	5	2	0.66
In salvage settings	4	0	
No transplant	85	14	
Complete response rate	79%	44%	$p < 0.01$
3 years PFS rate	78%	51%	$p = 0.06$
3 years OS rate	86%	71%	$p = 0.03$

Median follow-up time of survival patients: 35.4 months

Numbers may not add up to total patients for some characteristics because of unavailable information

SUV standard uptake value, *PS* Eastern Cooperative Oncology Group Performance Status, *LDH* serum lactate dehydrogenase level, *B symptoms* presence of at least one of the followings: night sweat, weight loss >10% over 6 months, and recurrent fever >38.3°C), *IPI* International Prognostic Index, *sIL2R* serum soluble interleukin-2 receptor level, *RT* radiotherapy, *ASCT* autologous stem cell transplant, *PFS* progression-free survival time, *OS* overall survival time, *LLN* lower limit of normal range

not found to be a significant parameter in the univariate analysis. All computations were performed in STATA version 9.0 (College Station, TX).

3 Results

3.1 Patient characteristics

Pretreatment characteristics of 110 patients with DLBCL are summarized in Table 1. The rationale for using cut-off value of 30 for SUVmax in this table is described later in the next subsection. The median age was 64 (range 21–86). None had human immunodeficiency virus (HIV-I/II) infection. Patients with diabetes mellitus were included in the study, but none had uncontrolled diabetes or was receiving insulin treatment. All patients received R-CHOP as the initial therapy. As a general rule, patients with limited stage contiguous disease were treated with three cycles of R-CHOP followed by radiotherapy, and those with advanced stage disease, limited stage non-contiguous disease were treated with eight cycles of R-CHOP, and radiotherapy was considered in patients with responding residual