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Safety, tolerability and pharmacokinetics of shorter duration of infusion of obinutuzumab in Japanese patients with B-cell non-Hodgkin lymphoma: final results of the phase II GATS study

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Abstract

Background: Shorter duration of infusion of monoclonal antibody treatments may reduce treatment burden and improve healthcare resource utilization.

Methods: This phase II study recruited Japanese patients with previously untreated CD20+ B-cell non-Hodgkin lymphoma. Patients received intravenous obinutuzumab 1000 mg by regular infusion on Days 1, 8 and 15 of Cycle 1, followed by 90-min shorter duration of infusion in up to seven subsequent cycles, provided they received ≥3 regular infusions without any grade ≥3 infusion-related reactions and had a lymphocyte count $<5.0 \times 10^9$ cells/l. Standard cyclophosphamide, doxorubicin, vincristine and prednisolone chemotherapy was given in Cycles 1–6. The primary endpoints were as follows: incidence of grade ≥3 infusion-related reactions in Cycle 2 in patients who started shorter duration of infusion in Cycle 2, serum obinutuzumab concentrations and pharmacokinetic parameters and the time course of cytokine release. Adverse events and serious adverse events were monitored.

Results: Of 35 patients treated, 28 completed eight cycles; 31 started shorter duration of infusion in Cycle 2 and two patients in subsequent cycles. Two patients discontinued before starting shorter duration of infusion. No grade ≥3 infusion-related reactions occurred in Cycle 2. Twenty-one infusion-related reactions (all grades 1–2) were reported in 17/35 (49%) patients overall, mostly in Cycle 1 (18/21 infusion-related reactions [86%]). Grade ≥3 AEs occurring in ≥10% of patients included neutropenia/neutrophil count decreased (66%) and leukopenia/white blood cell count decreased (23%). Steady-state pharmacokinetics of obinutuzumab were attained in Cycle 2 and

were not affected by shorter duration of infusion. No relevant cytokine elevations were reported with shorter duration of infusion.
Conclusions: Regular infusion and shorter duration of infusion of obinutuzumab have comparable tolerability and pharmacokinetics in Japanese patients.

Key words: Japanese, obinutuzumab, pharmacokinetics, safety

Introduction

Obinutuzumab is a glycoengineered, type II anti-CD20 monoclonal antibody indicated for the treatment of B-cell malignancies. It differs from its predecessor rituximab by having lower complement-dependent cytotoxicity but enhanced antibody-dependent cytotoxicity and direct B-cell death (1–3). In the phase III GALLIUM trial, which compared chemotherapy combined with either obinutuzumab or rituximab followed by anti-CD20 antibody maintenance therapy, obinutuzumab-based immunochemotherapy resulted in a clinically meaningful improvement in progression-free survival in patients with previously untreated follicular lymphoma (FL) (4,5). Obinutuzumab plus bendamustine followed by obinutuzumab maintenance also improved efficacy over bendamustine monotherapy in rituximab-refractory patients with indolent B-cell non-Hodgkin lymphoma (NHL) in the phase III GADOLIN study (6).

Obinutuzumab is currently given by intravenous (IV) infusion (7). Lengthy and/or frequent IV infusions are burdensome and inconvenient for patients and result in the need for lengthy observation times with increased nursing and administration staff workloads (8). Regular IV infusion (RI) of obinutuzumab takes approximately 3 to 4 h (7), and it is reasonable to consider that reducing the duration of infusion has potential advantages in terms of patient convenience, and more efficient use of healthcare facilities and staff time. The main potential disadvantage of a shorter duration of infusion (SDI) lies in the possibility of increased risk of infusion-related reactions (IRRs) mediated by cytokine release (9,10). However, studies in patients with rheumatoid arthritis or B-cell NHL have shown reduction of rituximab infusion times from at least 4 h to 1.5–2 h to be feasible (8,11), which has in turn led to the recommendation to increase infusion rates for rituximab (12) and, similarly, to the investigation of SDI in patients receiving obinutuzumab.

SDI was also investigated in the GATHER trial, a phase II, open-label, multicenter, single-arm study of obinutuzumab in combination with cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) chemotherapy in 80 previously untreated patients with CD20+ advanced diffuse large B-cell lymphoma (DLBCL) (12). Both of the SDI times evaluated in GATHER, 120 and 90 min, were well tolerated, with no IRRs of grade ≥3. Overall, 4% of the GATHER population was of Asian ethnicity, and ethnic differences in the frequency of polymorphisms in genes involved in drug metabolic pathways have been suggested to be associated with changes in enzyme activity that might affect drug pharmacokinetics (PK) (13). However, data obtained in various geographic populations receiving obinutuzumab have shown no relevant differences in the PK of obinutuzumab in Asian (including Chinese and Japanese) and non-Asian patients (14–16).

To explore these concepts further, the phase II GATS study (JO29737, JapicCTI-152 848) was carried out to investigate the tolerability of obinutuzumab given using SDI in previously untreated patients with CD20+ B-cell NHL, in particular the rate of grade ≥3 IRRs, and to evaluate serum obinutuzumab concentrations and PK, and the time course of cytokine release.

Patients and methods

Study design and treatments

This was a phase II, multicenter, open-label, single-arm study conducted in Japan. Eligible patients were aged ≥20 years with previously untreated and histologically confirmed CD20+ B-cell NHL (DLBCL, FL or marginal zone lymphoma); Eastern Cooperative Oncology Group performance status of 0–2; life expectancy ≥12 months from date of enrollment; adequate cardiovascular function defined as left ventricular ejection fraction ≥50%; adequate organ function defined as hemoglobin ≥9 g/dL, absolute neutrophil count $\geq 1.5 \times 10^9$ cells/l, peripheral lymphocytes $< 5.0 \times 10^9$ cells/l and platelet count $\geq 75 \times 10^9$ cells/l; serum bilirubin, serum creatinine and prothrombin time or activated partial thromboplastin time ≤1.5 times the site-specific upper limit and hepatic enzymes ≤2.5 times the site-specific upper limit. Patients were also required not to have undergone major surgery or to have received immune suppression therapy, live vaccine or other study drugs in the 4 weeks preceding enrollment; no monoclonal antibody treatment was permitted within the preceding 12 weeks.

Exclusion criteria included prior therapy for NHL (except for nodal biopsy or local irradiation); primary central nervous system (CNS) lymphoma, secondary CNS involvement or leptomeningeal lymphoma; recent (≤4 weeks) history of significant infection, other malignancy or history of autoimmune disease that could affect the results of the present study; ongoing corticosteroid treatment with the equivalent of prednisolone >30 mg/day for any condition other than lymphoma; any prior use of cytotoxic agents or rituximab or any other anti-CD20 antibody; positive tests for hepatitis B surface (HBs) antigen, HBs antibody, hepatitis B core (HBc) antibody, or hepatitis C virus (HCV) antibody; HIV or human T-cell lymphotropic virus type-I and uncontrolled diabetes mellitus. Patients with HBs antibodies clearly attributable to vaccination and who did not test positive for hepatitis B virus DNA regardless of antibody status were permitted to enroll, as were those who tested positive for HCV antibodies but who had HCV RNA-negative status.

The study was approved by local Institutional Review Boards and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. All patients gave written and informed consent.

Treatment consisted of eight 21-day cycles of obinutuzumab, given as 1 000 mg IV on Days 1, 8 and 15 of Cycle 1 plus standard CHOP on Day 1 of Cycles 1–6 (Supplementary data, Fig. 1). Obinutuzumab was administered as RI in Cycle 1 (3–4 h), and then as a 90-min SDI from Cycle 2 in patients who met the SDI criteria. The SDI criteria were to confirm patient safety at the RI rate and

included no grade ≥3 IRR with a causal relationship to obinutuzumab treatment during any of the three RIs in Cycle 1 and a peripheral lymphocyte count $<5.0 \times 10^9$ cells/l before SDI was started. Patients who did not meet these criteria before Cycle 2 could still transition from RI to SDI if they met the criteria in any subsequent cycle.

Standard CHOP consisted of cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2 and vincristine 1.4 mg/m^2 IV on Day 1, and prednisolone 100 mg/day orally or IV on Days 1–5. When obinutuzumab and CHOP were scheduled to be administered on the same day, prednisolone was given prior to the obinutuzumab infusion. Dose reductions to suit the patient's condition were permitted.

Study endpoints

The primary endpoints of the study were the incidence of grade ≥3 IRRs in Cycle 2 in patients who started SDI in Cycle 2, serum concentrations and PK parameters of obinutuzumab after SDI up to Day 12 of Cycle 2, and the time courses of cytokine release for tumor necrosis factor alpha (TNFα), interferon gamma (IFNγ) and interleukins 6, 8 and 10 (IL6, IL8 and IL10). IRRs were defined as adverse events (AEs) that were judged by the investigator to be related to obinutuzumab and that were reported during or within 24 h of an infusion.

Secondary endpoints included all other AEs (regardless of relationship to obinutuzumab treatment), IRRs reported during SDI, tumor response at the end of treatment and best response (at any time during follow-up).

The PK analysis population included all patients who received obinutuzumab by SDI on Cycle 2. PK parameters of obinutuzumab for each patient were estimated using non-compartmental analysis (NCA; Phoenix WinNonlin® version 6.4; Certara® USA, Inc.). The following PK parameters were calculated: maximum observed serum concentration (C_{max}), area under the serum concentration–time curve from 0 to Day 7 (AUC_{0-7}), elimination half-life ($t_{½}$) and AUC from 0 to last measurable point (AUC_{last}).

Statistical and analytical methods

The sample size was based on estimates of the true probability that the incidence of grade ≥3 IRRs in Cycle 2 would exceed 5%. According to the estimates used, on the assumption that there was a grade ≥3 IRR in 1 patient, if 30 patients were recruited, the likelihood that the probability of an IRR would exceed 5% would be 2.2%. This figure was increased to 36 on the assumption that 20% of patients would not be able to make the transition to SDI. The sample size was therefore set at 36 patients.

The incidence rate of grade ≥3 IRRs in Cycle 2 was obtained by dividing the number of patients who developed such reactions by the number of SDI-transition patients. The probability of a grade ≥3 IRR occurring was determined according to the Bayesian approach, using the incidence of grade ≥3 IRRs in Cycle 2 of the GATHER study as the prior distribution (Supplementary data). No differences were assumed to exist between Japanese and non-Japanese patients in the probability of developing a grade ≥3 IRR, regardless of infusion rate. We assumed that SDI was adequately tolerated if the true probability of developing a grade ≥3 IRR was ≤5%.

Summary statistics, including arithmetic mean, geometric mean, standard deviation, coefficient of variation, median, minimum and maximum, were calculated for cytokine concentrations at each study visit using serum cytokine concentrations from SDI-transition patients up to Cycle 2. Time courses of cytokine concentrations were also evaluated. The same summary data were generated for PK parameters based on serum obinutuzumab concentrations in SDI-transition patients up to Day 12 of Cycle 2. NCA was used. Cycle 2 serum concentrations were compared with additional samples obtained before and after dosing at Cycle 8.

Table 1. Patient and disease characteristics at baseline (safety population)

Characteristic	
Age, years	
Median (range)	66 (35–78)
<40	1 (3)
40–59	7 (20)
60–70	19 (54)
>70	8 (23)
Gender, male/female	
Male	23 (66)
Female	12 (34)
Cellular classification	
DLBCL	19 (54)
FL	13 (37)
Marginal zone lymphoma	1 (3)
Other[a]	2 (6)
ECOG PS at baseline	
0	28 (80)
1	6 (17)
2	1 (3)
Ann Arbor stage at baseline	
I	4 (11)
II	9 (26)
III	7 (20)
IV	15 (43)
FLIPI risk factors at baseline[b]	
1	4 (31)
2	7 (54)
3	2 (15)
IPI risk factors at baseline[c]	
0	2 (9)
1	7 (32)
2	5 (23)
3	3 (14)
4	4 (18)
5	1 (5)
B symptoms, *n*/*N*	
Weight loss	4 (11)
Fever	1 (3)
Night sweats	1 (3)
Bone marrow involvement	7 (20)
Spleen palpable	0 (0)
Mean lymphocyte count (SD), 10^9/l	1.375 (0.620)
Mean time from diagnosis to first infusion, months (SD)	109.5 (214.2)

ECOG PS, Eastern Cooperative Oncology Group performance status; FLIPI, Follicular Lymphoma International Prognostic Index; IPI, International Prognostic Index; *n*/*N*, number of patients with symptom/total number of patients for whom data are available; SD, standard deviation; FL, follicular lymphoma; DLBCL, diffuse large B-cell lymphoma.

Data are *n* (%) unless otherwise specified.

[a]Diagnosis of both FL and DLBCL.

[b]Patients with FL, *n* = 13.

[c]Patients with disease other than FL, *n* = 22.

Results

Patient population

In total, 36 Japanese patients were enrolled, of whom 35 were treated (safety population; Supplementary data, Fig. 2); 28 (80%) completed all eight cycles of treatment. Thirty-one patients started SDI in Cycle 2 (SDI-transition patients), and 2 further patients started SDI in subsequent cycles (1 in Cycle 3 and 1 in Cycle 4) to make a total of 33 SDI-treated patients. Two patients discontinued before starting SDI. Sufficient treatment intensity was achieved; median dose intensity of obinutuzumab was 100%.

The median age of the patients was 66 years, with just over half of the study population aged between 60 and 70 years (Table 1). Approximately two-thirds were male, and the majority of patients had DLBCL (54%) or FL (37%). A fifth of patients (20%) had bone marrow involvement.

Infusion-related reactions

Overall, 17/35 patients (49% of the safety population) experienced a total of 21 IRRs; all were grade 1 or 2, and the majority [18/21 IRRs (86%)] occurred during Cycle 1 (in which RI was used; Table 2). No SDI-associated IRRs occurred in SDI-transition patients in Cycle 2, so it was not possible to estimate the likelihood that the true probability of a grade ≥3 IRR in SDI-transition patients in Cycle 2 would exceed the 5% level inferred using the GATHER study data as the prior distribution. Furthermore, the likelihood that the true probability of a grade ≥3 IRR in SDI-transition patients in Cycle 2 would exceed the 5% level inferred using the non-informative prior distribution was 0.05%. There were reports of two patients with IRRs during the SDI in Cycles 6, 7 and 8; all were of grade 1 severity (1 patient experienced nasopharyngitis in Cycle 6, and another experienced headache in Cycles 7 and 8 and palpitations in Cycle 7). The only IRR with an incidence ≥10% was pyrexia (Table 2). IRRs reported in ≥5% of patients in any cycle included pyrexia, chills, nausea, blood pressure increase and headache (Table 2).

Other safety and tolerability endpoints

AEs were observed in all 35 patients (Table 3). All patients had at least one AE that was judged by the investigator to be treatment-related. Grade ≥3 AEs were observed in 30 patients (86%) and were judged treatment-related in 29 patients (83%). Blood and lymphatic system disorders (neutropenia, leukopenia and thrombocytopenia) were among the treatment-related grade ≥3 AEs most frequently reported (Table 3). Serious AEs were reported in nine patients (26%). All were judged treatment-related.

There were no AEs leading to death (grade 5) during the study. Obinutuzumab treatment was stopped in three patients because of AEs: one case each of infected dermal cyst, bronchiolitis and aspiration pneumonia. Aspiration pneumonia was not treatment-related. AEs leading to dose reduction or interruption of obinutuzumab treatment occurred in three patients, while AEs leading to dose reduction or interruption of any study drug occurred in nine patients. AEs leading to interruption of any study medication ($n = 4$) were neutropenia, cellulitis, IRR, cerebral infarction or pneumonitis (1 each). Dose reduction of any study medication ($n = 7$) was due to neutropenia/neutrophil count decreased ($n = 4$), leukopenia/white blood cell count decreased ($n = 3$), thrombocytopenia/platelet count decreased ($n = 3$), alanine aminotransferase increased, aspartate aminotransferase increased, neuropathy peripheral, peripheral sensory neuropathy or steroid withdrawal syndrome (1 each).

Pharmacokinetics

The mean serum obinutuzumab concentration at Cycle 8 was similar to that in Cycle 2 in 17 evaluable SDI-transition patients. This indicates that steady-state PK were attained at Cycle 2 and were not

Table 2. Summary of IRRs (safety population)

	Any-grade IRR in C1 (RI)	Grade ≥3 IRR in C1 (RI)	Any-grade IRR in C2–8 (SDI)	Grade ≥3 IRR in C2–8 (SDI)	Any-grade IRRs in C1–8	Grade ≥3 IRRs in C1–8
Patients with ≥1 IRR	17 (49)	2 (6)	2 (6)	0 (0)	17 (49)	2 (6)
Total number of IRRs	18	0	3	0	21	0
IRRs by PT						
Pyrexia	9 (26)	0 (0)	0	0 (0)	9 (26)	0 (0)
Chills	3 (9)	0 (0)	0	0 (0)	3 (9)	0 (0)
Nausea	2 (6)	0 (0)	0	0 (0)	2 (6)	0 (0)
Blood pressure increase	2 (6)	1 (3)	0	0 (0)	2 (6)	1 (3)
Headache	2 (6)	0 (0)	1 (3)[a]	0 (0)	2 (6)	0 (0)
Vomiting	1 (3)	0 (0)	0	0 (0)	1 (3)	0 (0)
Blood pressure decrease	1 (3)	0 (0)	0	0 (0)	1 (3)	0 (0)
Cerebral infarction	1 (3)	0 (0)	0	0 (0)	1 (3)	0 (0)
Hypoxia	1 (3)	0 (0)	0	0 (0)	1 (3)	0 (0)
Wheezing	1 (3)	0 (0)	0	0 (0)	1 (3)	0 (0)
Thrombocytopenia	1 (3)	1 (3)	0	0 (0)	1 (3)	1 (3)
Palpitations	0	0 (0)	1 (3)	0 (0)	1 (3)	0 (0)
Nasopharyngitis	0	0 (0)	1 (3)	0 (0)	1 (3)	0 (0)
Hyperkalemia	1 (3)[b]	0 (0)	0	0 (0)	1 (3)	0 (0)
Pruritus	1 (3)	0 (0)	0	0 (0)	1 (3)	0 (0)

C, cycle; D, day; IRR, infusion-related reaction; PT, preferred term; RI, regular infusion; SDI, shorter duration of infusion.

Data are *n* (%) unless otherwise specified.

[a]This patient experienced two separate occurrences of headache during C7 and C8.

[b]This patient experienced two separate occurrences of hyperkalemia on C1D8 and C1D15.

Table 3. Summary of AEs (safety population)

	Any grade	Grade ≥3	SAEs
Patients with ≥1 AE	35 (100)	30 (85.7)	9 (26)
IRR	17 (49)	0 (0)	1 (3)
Peripheral sensory neuropathy	17 (49)	0 (0)	0 (0)
Nausea	17 (49)	0 (0)	0 (0)
Constipation	15 (43)	0 (0)	0 (0)
Neutropenia[a]	23 (66)	23 (66)	0 (0)
Pyrexia	12 (34)	0 (0)	0 (0)
Dysgeusia	11 (31)	0 (0)	0 (0)
Alopecia	10 (29)	0 (0)	0 (0)
Decreased appetite	9 (26)	0 (0)	0 (0)
Insomnia	8 (23)	0 (0)	0 (0)
Neuropathy peripheral	7 (20)	0 (0)	0 (0)
Stomatitis	6 (17)	0 (0)	0 (0)
Thrombocytopenia[b]	9 (26)	4 (11)	0 (0)
Malaise	5 (14)	0 (0)	0 (0)
Leukopenia[c]	8 (23)	8 (23)	0 (0)
Febrile neutropenia	6 (17)	6 (17)	2 (6)
Back pain	4 (11)	0 (0)	0 (0)
Herpes zoster	3 (9)	1 (3)	1 (3)
Cellulitis	2 (6)	2 (6)	2 (6)
Bacteremia	1 (3)	1 (3)	1 (3)
Gastroenteritis	1 (3)	1 (3)	1 (3)
Pneumonia	1 (3)	1 (3)	1 (3)
Pneumonia aspiration	1 (3)	1 (3)	1 (3)
Pneumonitis	1 (3)	1 (3)	1 (3)
Cataract	1 (3)	1 (3)	1 (3)
Cerebral infarction	1 (3)	0 (0)	1 (3)
Depression	1 (3)	1 (3)	1 (3)

AE, adverse event; SAE, serious adverse event.

Data are *n* (%) unless otherwise specified.

AEs displayed for preferred terms that had an incidence of ≥10% (any grade) and/or ≥5% (grade ≥3) and/or ≥2% (SAE).

[a]Includes the preferred terms neutropenia and neutrophil count decreased.

[b]Includes the preferred terms thrombocytopenia and platelet count decreased.

[c]Includes the preferred terms leukopenia and white blood cell count decreased.

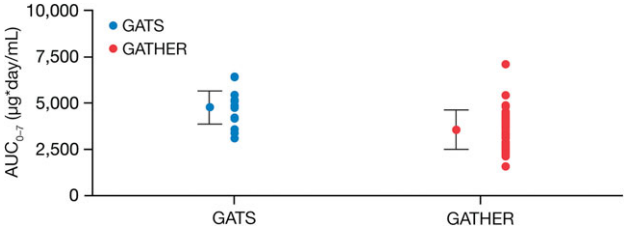

Figure 1. Comparison of AUC_{last} (AUC_{7day}) after SDI administration of obinutuzumab between GATS (Cycle 2) and GATHER (Cycle 8) studies. Values are mean ± SD, individual. AUC_{0-7}, area under the serum concentration–time curve from 0 to Day 7; SD, standard deviation; SDI, shorter duration of infusion.

affected by the reduced duration of infusion. The mean ± standard deviation AUC_{last} (AUC_{7day}) was 4 770 ± 898 µg day/ml at Cycle 2 (vs. 3 590 ± 1060 µg day/ml at Cycle 8 in GATHER) (Fig. 1). The mean $t_{½}$ was 15.4 ± 7.55 days (based on 17 evaluable SDI patients; vs. 23.0 ± 15 days in GATHER). The AUC_{last} (AUC_{11day}) value on Day 1 of Cycle 2 was 6 790 ± 1450 µg day/ml, with a C_{max} of 925 ± 221 µg/ml.

Table 4. Treatment efficacy

Category	Without PET		With PET	
	Response at the end of treatment	Best response	Response at the end of treatment	Best response
FL	(*n* = 13)		(*n* = 4)	
Responders[a]	**10 (77) [46–95]**	**12 (92) [64–100]**	**3 (75) [19–99]**	**3 (75) [19–99]**
Non-responders	**3 (23)**	**1** (8)	**1 (25)**	**1 (25)**
Complete response[a]	8 (62) [32–86]	8 (62) [32–86]	3 (75) [19–99]	3 (75) [19–99]
Partial response[a]	2 (15) [2–45]	4 (31) [9–61]	0 [0–60]	0 [0–60]
Stable disease[a]	1 (8) [0–36]	1 (8) [0–36]	0 [0–60]	0 [0–60]
Progressive disease[a]	2 (15) [2–45]	0 [0–25]	1 (25) [1–81]	1 (25) [1–81]
Missing or not evaluable	0	0	0	0
DLBCL	(*n* = 19)		(*n* = 8)	
Responders[a]	**13 (68) [43–87]**	**15 (79) [54–94]**	**8 (100) [63–100]**	**8 (100) [63–100]**
Non-responders	**6 (32)**	**4** (21)	**0**	**0**
Complete response[a]	11 (58) [34–80]	12 (63) [38–84]	7 (88) [47–100]	7 (88) [47–100]
Partial response[a]	2 (11) [1–33]	3 (16) [3–40]	1 (13) [0–53]	1 (13) [0–53]
Stable disease[a]	0 [0–18]	1 (5) [0–26]	0 [0–37]	0 [0–37]
Progressive disease[a]	4 (21) [6–46]	1 (5) [0–26]	0 [0–37]	0 [0–37]
Missing or not evaluable	2 (11)	2 (11)	0	0

CI, confidence interval; PET, positron emission tomography.

Data are *n* (%) [95% CI] unless otherwise specified.

[a]Pearson–Clopper CI.

Cytokines

For all 35 patients (including the 31 SDI-transition patients), cytokine elevations were observed during the first obinutuzumab infusion but were followed by an immediate decrease 2–5 h after the end of the infusion. No relevant changes were observed after starting SDI (Supplementary data, Fig. 3). There was also a rapid depletion in CD19+ B-cells after the first obinutuzumab infusion (i.e. B-cell depletion; Supplementary data, Fig. 4). Counts decreased to $<0.07 \times 10^9$ cells/l and remained at this level for the duration of the study.

Efficacy

The overall response rate on computed tomography-based assessment at the end of treatment was 77% (10/13) in patients with FL and 68% (13/19) in patients with DLBCL (including complete and partial responses; Table 4). The best overall responses were 92% (12/13) and 79% (15/19), respectively (Table 4). Complete responses (without positron emission tomography scanning) were obtained in 8 of 13 patients with FL (62%) and 11 of 19 patients with DLBCL (58%) at the end of treatment, and in 8 of 13 patients with FL (62%) and 12 of 19 patients with DLBCL (63%) in the best complete response evaluation (Table 4).

Discussion

The current study aimed to investigate the tolerability (in particular the rate of IRRs), PK and cytokine release profile of SDI of obinutuzumab plus CHOP chemotherapy in patients with untreated CD20+ B-cell NHL. The vast majority of IRRs with obinutuzumab plus CHOP were observed in Cycle 1 of treatment, during which RI was used. No IRRs of any grade were observed during Cycle 2, and only two patients experienced IRRs in subsequent cycles during treatment with obinutuzumab by SDI, which were all grade 1.

The observed rate of IRRs (49%) is concordant with other reports of obinutuzumab given by RI. Although this is not a direct comparison, it suggests that there is no increased risk of IRRs in patients treated with SDI obinutuzumab. In the phase III GALLIUM trial of obinutuzumab- vs. rituximab-based immunochemotherapy in 1 202 previously untreated patients with FL, IRRs were the most common any-grade AEs (68% of obinutuzumab chemotherapy-treated patients) and grade ≥3 AEs (12% of obinutuzumab chemotherapy-treated patients) and typically occurred during the first infusion (4). Similarly, in the phase III GOYA study of 1 418 patients with untreated DLBCL, IRRs occurred in 45% (any grade) and 10% (grade ≥3) of patients receiving obinutuzumab with CHOP (17). In the phase Ib GAUDI study, IRRs occurred in 18 of 28 patients (64%) receiving obinutuzumab plus CHOP; although this occurrence is more common than in the current study, IRRs were also mainly restricted to the first infusion, and grade 3–4 IRRs were infrequent, occurring in two patients (7%) (18). IRRs have also predominated in studies in patients with B-cell malignancies in which obinutuzumab has been trialed as monotherapy, with the majority of reactions being grade 1 or 2 (15,19–22). Notably, in the GATHER study in 100 mainly non-Asian patients with DLBCL who received obinutuzumab plus CHOP, no grade ≥3 IRRs were noted in patients who received SDI over 120 or 90 min (12). The pattern of IRRs seen in GATHER was similar to GATS, with most reactions (77%) occurring during Cycle 1 (during which RI was given). Other safety and tolerability findings were similar between the GATHER and GATS populations (12). No new safety signals were identified in the current study.

PK and serum cytokine data were also found to be comparable with the results of the GATHER study (12). Exposure to obinutuzumab after SDI was also of the same order in the current study as in GATHER, with similar AUC_{0-7} and $t_{1/2}$ values (12). The AUC_{last} value reported in the present study from Day 1 of Cycle 2 (4 770 ± 885 μg day/ml) is also of the same order of the AUC_{last} reported by Ogura et al. (15) on Day 8 of Cycle 1 in patients who received obinutuzumab 800 mg (4 190 ± 1190 μg day/ml) or 1 200 mg (6 540 ± 1070 μg day/ml) in their dose-finding phase I study in 12 Japanese patients with relapsed or refractory B-cell NHL.

Patterns of inflammatory cytokine release, with rapid peaking during the first infusion followed by a rapid reduction and stabilization at baseline levels, were also similar to previous reports. The phase II GAUSS study in 175 patients with relapsed indolent B-cell NHL (19) showed peak cytokine levels of IL6, IL8, IL10, TNFα and IFNγ that were notably elevated during the first infusion of obinutuzumab but then returned to baseline without any increase during subsequent infusions. The same pattern was reported in the phase I/II GAUGUIN study in the cohort of 33 patients with relapsed or refractory CLL (22). We note, as did the authors of GAUGUIN (22), that these early elevations in inflammatory cytokine levels coincide with the increased rates of reporting of IRRs during the first cycle of treatment in GATS and the other studies mentioned. The pattern of CD19+ B-cell response was also similar to previous reports. Ogura et al. (15) showed a rapid reduction after the first infusion of obinutuzumab, with the nadir achieved in most patients after infusion on Day 1. The same rapid B-cell depletion was reported in Cycle 1 of GAUGUIN in the CLL cohort (22) and the indolent B-cell NHL cohort (20).

Overall and complete response rates at the end of treatment in patients with DLBCL (68 and 58%, respectively) were of the same order as those obtained in GATHER (82 and 55%, respectively), in which SDI was also used (12) for patients with DLBCL. There are no data available yet for response rates in FL patients treated with obinutuzumab using SDI for comparison.

A limitation of the current study lies in the small patient population; a much larger sample would be required for definitive assessment of safety of obinutuzumab SDI, although the results obtained do appear concordant with previous findings in both Japanese patients and those undergoing treatment with SDI. We note also that the GATS study lacked a control arm in which, for example, patients might have received a conventional full set of cycles of obinutuzumab by RI in addition to CHOP.

In conclusion, obinutuzumab given by SDI was well tolerated in this Japanese patient cohort. No SDI-associated IRRs were observed in the second cycle of treatment (i.e. the first SDI cycle); a small number of IRRs were observed with SDI in later cycles but were tolerable and manageable. The rate of IRRs was in line with findings from other studies of obinutuzumab given by RI, indicating that there is no increased risk of IRRs when obinutuzumab is given by SDI. Overall, the findings suggest that obinutuzumab can be administered safely by SDI.

Supplementary data

Supplementary data are available at *Japanese Journal of Clinical Oncology* online.

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References

1. Mössner E, Brünker P, Moser S, et al. Increasing the efficacy of CD20 antibody therapy through the engineering of a new type II anti-CD20 antibody with enhanced direct and immune effector cell-mediated B-cell cytotoxicity. *Blood* 2010;115:4393–402.
2. Herter S, Herting F, Mundigl O, et al. Preclinical activity of the type II CD20 antibody GA101 (obinutuzumab) compared with rituximab and ofatumumab in vitro and in xenograft models. *Mol Cancer Ther* 2013;12:2031–42.
3. Tobinai K, Klein C, Oya N, Fingerle-Rowson G. A review of obinutuzumab (GA101), a novel type II anti-CD20 monoclonal antibody, for the treatment of patients with B-cell malignancies. *Adv Ther* 2017;34:324–56.
4. Marcus R, Davies A, Ando K, et al. Obinutuzumab for the first-line treatment of follicular lymphoma. *N Engl J Med* 2017;377:1331–44.
5. Hiddemann W, Barbui AM, Canales Albendea MA, et al. Immunochemotherapy with obinutuzumab or rituximab in previously untreated folllicular lymphoma in the randomised phase III GALLIUM study: analysis by chemotherapy regimen. *Hematol Oncol* 2017;35:117–9.
6. Sehn LH, Chua N, Mayer J, et al. Obinutuzumab plus bendamustine versus bendamustine monotherapy in patients with rituximab-refractory indolent non-Hodgkin lymphoma (GADOLIN): a randomised, controlled, open-label, multicentre, phase 3 trial. *Lancet Oncol* 2016;17:1081–93.
7. Food and Drug Administration. *GAZYVA® (obinutuzumab) injection, for intravenous infusion*. South San Francisco, CA: Genentech, Inc, 2016.
8. Pritchard CH, Greenwald MW, Kremer JM, et al. Safety of infusing rituximab at a more rapid rate in patients with rheumatoid arthritis: results from the RATE-RA study. *BMC Musculoskelet Disord* 2014;15:177.
9. Winkler U, Jensen M, Manzke O, Schulz H, Diehl V, Engert A. Cytokine-release syndrome in patients with B-cell chronic lymphocytic leukemia and high lymphocyte counts after treatment with an anti-CD20 monoclonal antibody (rituximab, IDEC-C2B8). *Blood* 1999;94:2217–24.
10. Freeman CL, Morschhauser F, Sehn L, et al. Cytokine release in patients with CLL treated with obinutuzumab and possible relationship with infusion-related reactions. *Blood* 2015;126:2646–9.
11. Dakhil S, Hermann R, Schreeder MT, et al. Phase III safety study of rituximab administered as a 90-minute infusion in patients with previously untreated diffuse large B-cell and follicular lymphoma. *Leuk Lymphoma* 2014;55:2335–40.
12. Zelenetz AD, Forero-Torres A, Costa LJ, et al Safety and Efficacy of Obinutuzumab (GA101) Plus CHOP Chemotherapy in First-Line Advanced Diffuse Large B-Cell Lymphoma: Results from the Phase 2 GATHER Study. In preparation.
13. Phan VH, Tan C, Rittau A, Xu H, McLachlan AJ, Clarke SJ. An update on ethnic differences in drug metabolism and toxicity from anti-cancer drugs. *Expert Opin Drug Metab Toxicol* 2011;7:1395–410.
14. Cartron G, Hourcade-Potelleret F, Morschhauser F, et al. Rationale for optimal obinutuzumab/GA101 dosing regimen in B-cell non-Hodgkin lymphoma. *Haematologica* 2016;101:226–34.
15. Ogura M, Tobinai K, Hatake K, et al. Phase I study of obinutuzumab (GA101) in Japanese patients with relapsed or refractory B-cell non-Hodgkin lymphoma. *Cancer Sci* 2013;104:105–10.
16. Zhai J, Qin Y, Zhu J, et al. Pharmacokinetics of obinutuzumab in Chinese patients with B-cell lymphomas. *Br J Clin Pharmacol* 2017;83:1446–56.
17. Vitolo U, Trněný M, Belada D, et al. Obinutuzumab or rituximab plus CHOP in previously untreated DLBCL. *J Clin Oncol* 2017;35:3529–37. doi:10.1200/JCO.2017.73.3402.
18. Radford J, Davies A, Cartron G, et al. Obinutuzumab (GA101) plus CHOP or FC in relapsed/refractory follicular lymphoma: results of the GAUDI study (BO21000). *Blood* 2013;122:1137–43.
19. Sehn LH, Goy A, Offner FC, et al. Randomized phase II trial comparing obinutuzumab (GA101) with rituximab in patients with relapsed CD20+ indolent B-cell non-Hodgkin lymphoma: final analysis of the GAUSS study. *J Clin Oncol* 2015;33:3467–74.
20. Salles GA, Morschhauser F, Solal-Celigny P, et al. Obinutuzumab (GA101) in patients with relapsed/refractory indolent non-Hodgkin lymphoma: results from the phase II GAUGUIN study. *J Clin Oncol* 2013;31:2920–6.
21. Morschhauser FA, Cartron G, Thieblemont C, et al. Obinutuzumab (GA101) monotherapy in relapsed/refractory diffuse large b-cell lymphoma or mantle-cell lymphoma: results from the phase II GAUGUIN study. *J Clin Oncol* 2013;31:2912–9.
22. Cartron G, de Guibert S, Dilhuydy MS, et al. Obinutuzumab (GA101) in relapsed/refractory chronic lymphocytic leukemia: final data from the phase 1/2 GAUGUIN study. *Blood* 2014;124:2196–202.