Clinical Cancer Research

Phase I Study of Inotuzumab Ozogamicin Combined with R-CVP for Relapsed/Refractory CD22+ B-cell Non-Hodgkin Lymphoma

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Abstract

Purpose: To evaluate the safety, preliminary efficacy, and pharmacokinetics of inotuzumab ozogamicin, an anti-CD22 antibody conjugated to calicheamicin, in combination with the immunochemotherapeutic regimen, rituximab, cyclophosphamide, vincristine, and prednisone (R-CVP), in patients with relapsed/refractory CD22+ B-cell non-Hodgkin lymphoma (NHL).

Experimental Design: In part 1 ($n = 16$), patients received inotuzumab ozogamicin plus R-CVP on a 21-day cycle with escalating doses of cyclophosphamide first then inotuzumab ozogamicin. Part 2 ($n = 10$) confirmed the safety and tolerability of the maximum tolerated dose (MTD), which required a dose-limiting toxicity rate of <33% in cycle 1 and <33% of patients discontinuing before cycle 3 due to treatment-related adverse events (AEs). Part 3 ($n = 22$) evaluated the preliminary efficacy of inotuzumab ozogamicin plus R-CVP.

Results: The MTD was determined to be standard-dose R-CVP plus inotuzumab ozogamicin 0.8 mg/m^2. The most common treatment-related grade ≥3 AEs in the MTD cohort ($n = 38$) were hematologic: neutropenia (74%), thrombocytopenia (50%), lymphopenia (42%), and leukopenia (47%). Among the 48 patients treated in the study, 13 discontinued due to AEs, most commonly thrombocytopenia ($n = 10$). Overall, 13 patients died, including one death due to treatment-related pneumonia secondary to neutropenia. Among patients receiving the MTD ($n = 38$), the overall response rate (ORR) was 84% ($n = 32$), including 24% ($n = 9$) with complete response; the ORR was 100% for patients with indolent lymphoma ($n = 27$) and 57% for those with aggressive histology lymphoma ($n = 21$).

Conclusions: Inotuzumab ozogamicin at 0.8 mg/m^2 plus full dose R-CVP was associated with manageable toxicities and demonstrated a high rate of response in patients with relapsed/refractory CD22+ B-cell NHL. The study is registered at ClinicalTrials.gov (NCT01055496). *Clin Cancer Res; 22(19); 4807–16. ©2016 AACR.*

Introduction

Non-Hodgkin lymphoma (NHL) is estimated to be the sixth most common newly diagnosed cancer in the United States in 2015 (1). Although mAb-based therapies have advanced the treatment of many lymphoma subtypes (particularly B-cell NHL), relapse rates are high, and many patients are refractory to therapy (2–6). Combination treatments consisting of mAbs and chemotherapeutics have successfully treated relapsed/refractory NHL; however, toxicity remains a significant limitation with these regimens (7–9). Combination therapies that are both safe and effective are needed to meet the challenges of treating relapsed/refractory NHL.

The CD22 antigen is expressed by >90% of B-cell NHLs, is rapidly internalized, and is not shed into the extracellular environment (10–13). As such, it is an ideal target for mAb-based therapy for B-cell malignancies (10, 11). Inotuzumab ozogamicin (CMC-544) is a humanized immunoglobulin G4 anti-CD22 mAb conjugated to a derivative of calicheamicin, a potent cytotoxic antibiotic (12). Upon binding to inotuzumab ozogamicin, CD22 is rapidly internalized, releasing calicheamicin, which binds to DNA and induces double-strand DNA breaks, resulting in apoptosis (14–17). In contrast, the mechanism of action of the anti-CD20 mAb, rituximab, involves activation of immune system defense mechanisms, as well as directly inducing apoptosis (18). These disparate mechanisms of action allow for the possibility of synergistic effects between inotuzumab ozogamicin and rituximab; such effects have been observed in preclinical studies (19).

Previous phase I studies of inotuzumab ozogamicin demonstrated preliminary activity and manageable toxicity in patients

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Translational Relevance

There is a need for safe and effective combination therapies that meet the challenges of treating relapsed/refractory non-Hodgkin lymphoma (NHL). Preclinical studies suggest that the different mechanisms of action of anti-CD22 mAb inotuzumab ozogamicin and anti-CD20 mAb rituximab allow for synergistic effects. Moreover, the use of inotuzumab ozogamicin with chemotherapeutics is supported by preclinical study evidence. This phase I study determined the MTD and evaluated the safety and preliminary efficacy of inotuzumab ozogamicin combined with rituximab, cyclophosphamide, vincristine, and prednisone (R-CVP) in patients with relapsed/refractory CD22+ B-cell NHL. Results suggest that inotuzumab ozogamicin 0.8 mg/m^2 given with standard-dose R-CVP demonstrated manageable safety and tolerability. Nearly all grade 3/4 adverse events were hematologic, most commonly thrombocytopenia and neutropenia. Antitumor activity was observed. Further studies in larger populations are required to determine whether this regimen offers an advantage over previously established regimens or whether inotuzumab ozogamicin should be combined with other agents.

with relapsed/refractory B-cell NHL (20–22). In addition, inotuzumab ozogamicin plus rituximab demonstrated preliminary activity in patients with relapsed/refractory B-cell NHL without a significant increase in toxicity (22, 23). Additive antitumor activity was observed in xenograft models with inotuzumab ozogamicin in combination with chemotherapeutics, such as cyclophosphamide, vincristine, and prednisone (CVP) (24). The alkylating agent–based immunotherapeutic regimen consisting of rituximab plus CVP (R-CVP) is approved for the treatment of previously untreated patients with stage III/IV follicular lymphoma in both Europe and in the United States (25). Treatment choice in relapsed patients depends on prior treatment history, type of lymphoma, and local treatment practices (26, 27). This phase I study determined the MTD and evaluated the safety and preliminary efficacy of inotuzumab ozogamicin given in combination with R-CVP in patients with relapsed/refractory CD22+ B-cell NHL.

Patients and Methods

Patients

Eligible patients were aged ≥18 years, with a diagnosis of CD22+ B-cell NHL (Table 1). Patients were required to have an Eastern Cooperative Oncology Group performance status of ≤2; total bilirubin ≤upper limit of normal (ULN; in patients without Gilbert disease); aspartate and alanine aminotransferase (AST and ALT) ≤2.5 × ULN; serum creatinine ≤2 × ULN and a urine protein/creatinine ratio of ≤0.5; an absolute neutrophil count ≥1.0 × 10^9/L (1,000/μL) and a platelet count ≥100 × 10^9/L; and ≥1 measurable disease lesion >1 cm in diameter (product diameter ≥2.25 cm^2 by CT or MRI). Patients in the dose-escalation cohorts had ≥1 prior anticancer treatment, including prior rituximab and chemotherapy. Enrollment of previously untreated patients in the MTD confirmation and preliminary efficacy cohorts was permitted if they were not considered candidates for anthracycline-based therapy.

Key exclusion criteria included the following: >3 previous chemotherapy regimens containing ≥2 cytotoxic agents; treatment with anti-CD22 antibodies, radioimmunotherapy or autologous transplant within 6 months of the first dose of study drugs; chemotherapy, cancer-immunosuppressive therapy, radiotherapy, growth factors (except for erythropoietin), or investigational agents within 28 days of first dose of study drugs. Also excluded were candidates for hematopoietic stem cell transplant; patients with a Fridericia corrected QT interval >470 msec at screening, symptomatic central nervous system disease, or a history of veno-occlusive disease/sinusoidal obstruction syndrome or chronic liver disease.

Written informed consent was obtained from each participant prior to study-related activities. The study (ClinicalTrials.gov: NCT01055496) was conducted in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice and the Declaration of Helsinki. Institutional Review Boards and/or independent ethics committees at each participating center reviewed and approved the study protocol.

Study design and drug administration

This open-label study was conducted at 12 centers in seven countries; patients were enrolled from March 2010 to February 2012. The study ascertained the safety, tolerability, and MTD (primary objective), as well as the preliminary efficacy and pharmacokinetics (secondary objectives) of inotuzumab ozogamicin given in combination with R-CVP in patients with relapsed/refractory CD22+ B-cell NHL. The study consisted of 3 parts: MTD determination (part 1), MTD confirmation (part 2), and MTD expansion (part 3). Patients received rituximab 375 mg/m^2 i.v., cyclophosphamide 375 to 750 mg/m^2 i.v., and vincristine 1.4 mg/m^2 (2 mg maximum) i.v. on day 1 plus prednisone 40 mg/m^2 on days 1 to 5, as well as inotuzumab ozogamicin 0.8 or 1.3 mg/m^2 i.v. on day 2 of each 21-day cycle (±2 days). Treatment continued for a maximum of 6 cycles unless there was evidence of progressive disease (PD) or prolonged or excessive toxicity; dose escalation was based on a toxicity assessment during cycle 1.

In part 1, dose escalation of cyclophosphamide (3 levels) or inotuzumab ozogamicin (2 levels) using a standard 3+3 design was used to determine the MTD (Supplementary Text and Supplementary Table S1). Initially, only the dose of cyclophosphamide was increased. Because the full dose of cyclophosphamide was tolerated, inotuzumab ozogamicin was increased to 1.3 mg/m^2. Ten additional patients were enrolled in part 2 to confirm the safety and tolerability of the MTD (cyclophosphamide 750 mg/m^2 and inotuzumab ozogamicin 0.8 mg/m^2). Cohorts and treatment schedules are shown in Fig. 1. An additional 22 patients were enrolled in part 3. The preliminary safety and antitumor activity of inotuzumab ozogamicin plus R-CVP at the MTD was further examined in both parts 2 and 3.

Safety, efficacy, and pharmacokinetic analyses

Safety assessments included physical examination, vital signs, electrocardiograms, laboratory test measurements, and adverse event (AE) reporting. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 and were monitored for ≥4 to 6 weeks after last dose (end-of-treatment visit). All treatment-related AEs were monitored until resolved, return to baseline, or stable condition. Disease assessments were performed until PD, initiation of a new

anticancer therapy, or death; follow-up for survival continued for up to 2 years from the first dose of study drug.

Response and progression status were assessed using a modification of the International Working Group Criteria (28). Efficacy endpoints included the overall (objective) response [OR; complete response (CR) plus partial response (PR)], progression-free survival (PFS), overall survival (OS), and duration of response (DOR). Tumor responses were evaluated using objective measurements of tumor masses from MRI and CT scans, clinical information, B-symptoms, laboratory assessments, and biochemical markers of disease activity. Tumor site and measurements were determined at screening, every 9 weeks during the active period (or earlier if there was evidence of tumor response or progression), at the end-of-treatment visit, and then every 12 to 24 weeks until disease progression or new anticancer therapy or death for up to 2 years after the first dose of study drug.

Determination of pharmacokinetics included measurements of inotuzumab ozogamicin, total calicheamicin (conjugated plus unconjugated forms), and unconjugated calicheamicin concentrations in serum, which were collected during cycle 1 at 0 hour (predose), and during cycle 3 at 0 (predose), 1, 3, 24, and 144 hours after inotuzumab ozogamicin treatment. Serum samples to detect anti-inotuzumab ozogamicin and anti-rituximab antibodies were also obtained 24 hours predose during cycles 1, 4, and at the end of treatment. All analyses were performed using appropriately validated ELISA. For pharmacokinetic measures, analytes were quantified with limits of quantitation of 52.2, 5, and 1.25 ng/mL for inotuzumab ozogamicin, total calicheamicin, and unconjugated calicheamicin, respectively.

Statistical analysis

This preliminary study enrolled a limited number of subjects primarily to assess safety. The sample size was determined by clinical rather than statistical considerations. An analysis was performed for the 10 patients in the MTD confirmation cohort, and the decision to proceed to part 3 was based on information available from the unlocked database at the time of this analysis. Continuation of the study to part 3 required a CR or PR in $\geq$2 patients, <33% of patients experiencing a dose-limiting toxicity (DLT), and <33% unable to receive $\geq$3 cycles due to a drug-related toxicity. Outcomes are reported on the basis of final data for all treated patients. PFS, OS, and DOR distributions were summarized using the Kaplan–Meier method.

Results

Patients

Forty-eight patients (indolent, $n = 27$; aggressive, $n = 21$) were enrolled in the study (Fig. 1); baseline patient demographics and disease characteristics are presented in Table 1. Patients had

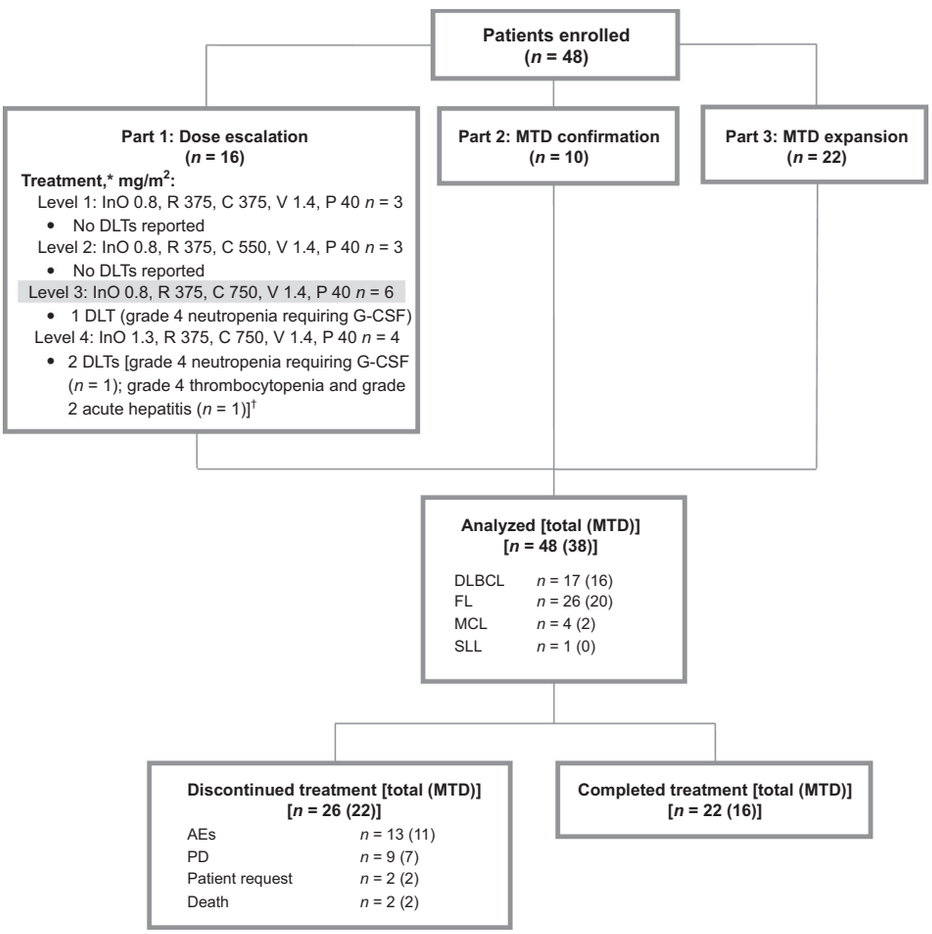

Figure 1.
Patient disposition. C, cyclophosphamide; FL, follicular lymphoma; InO, inotuzumab ozogamicin; MCL, mantle cell lymphoma; P, prednisone; R, rituximab; SLL, small lymphocytic lymphoma; V, vincristine. Shading indicates the dose level further evaluated as the MTD. *, All patients received inotuzumab ozogamicin on day 2, rituximab, cyclophosphamide, and vincristine on day 1, and prednisone on days 1 to 5. †, One patient was not evaluable for DLTs due to incorrect inotuzumab ozogamicin dose administered during cycle 1.

Table 1. Patient demographics and baseline characteristics

Characteristics	Safety population ($N = 48$)
Median age (range), y	63 (42–81)
Male, *n* (%)	27 (56)
Race, *n* (%)	
Asian	28 (58)
White	20 (42)
Histologic subtype[a], *n* (%)	
FL	26 (54)
DLBCL	17 (35)
MCL	4 (8)
SLL	1 (2)
ECOG performance status, *n* (%)	
0	35 (73)
1	9 (19)
2	4 (8)
IPI score[b], *n* (%)	
0	0
1	5 (10)
2	3 (6)
3	8 (17)
4	5 (10)
5	1 (2)
FLIPI score[c], *n* (%)	
0	5 (10)
1	9 (19)
2	8 (17)
3	3 (6)
4	0
5	1 (2)
Stage III/IV disease, *n* (%)	32 (67)
Prior antilymphoma treatment regimens, *n* (%)	
0	1 (2)
1	19 (40)
2	16 (33)
3	7 (15)
≥4	5 (10)
Median (range)	2 (1–6)
Prior radiotherapy, *n* (%)	14 (29)
Prior anthracyclines, *n* (%)	42 (88)
Prior aSCT, *n* (%)	3 (6)
Best response to most recent prior therapy, *n* (%)	
CR	20 (42)
PR	14 (29)
Stable disease	4 (8)
Disease progression	4 (8)
Unknown	5 (10)
Missing	1 (2)

Abbreviations: aSCT, autologous stem cell transplantation; ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index (for follicular lymphoma only); IPI, International Prognostic Index (for subtypes other than FL); MCL, mantle cell lymphoma; SLL, small lymphocytic lymphoma.

[a]Disease at screening (stage IA, $n = 6$; stage IIA, $n = 10$; stage IIIA/B, $n = 12$; stage IVA/B, $n = 20$).

[b]Includes patients with all histologic subtypes, except follicular lymphoma ($n = 22$).

[c]Includes only patients with follicular lymphoma ($n = 26$).

follicular lymphoma (54%), diffuse large B-cell lymphoma (DLBCL; 35%), mantle cell lymphoma (8%), or small lymphocytic leukemia (2%) at screening and had received a median of two prior therapies (range, 1–6). All patients received prior anticancer therapy that included rituximab except for one patient enrolled in part 3. Eight patients (indolent, $n = 3$; aggressive, $n = 5$) had refractory disease at baseline (best response to most recent prior therapy was stable or progressive disease).

All patients received ≥1 dose of study treatment and most (52% total; 50% at the MTD) completed all six treatment cycles with a median (range) of six (1–6) cycles completed (one patient did not receive vincristine during the last two treatment cycles). Reasons for discontinuing treatment included AEs [$n = 13$ (27%)], PD [$n = 9$ (19%)], patient request [$n = 2$ (4%)], and death [$n = 2$ (4%)].

MTD determination and confirmation

In part 1 (dose escalation), the MTD was determined to be inotuzumab ozogamicin 0.8 mg/m^2 given on day 2 with standard-dose R-CVP (rituximab 375 mg/m^2, cyclophosphamide 750 mg/m^2, and vincristine 1.4 mg/m^2 all on day 1, and prednisone 40 mg/m^2 on days 1–5) intravenously every 21 days (29). DLTs observed among the 16 patients treated in part 1 are summarized in Fig. 1. No DLTs were reported with inotuzumab ozogamicin 0.8 mg/m^2 at the lower doses of cyclophosphamide (levels 1 and 2; $n = 3$ each). One of six patients at dose level 3 experienced a DLT (grade 4 neutropenia requiring G-CSF); two of four patients reported DLTs at dose level 4 (one patient had grade 4 neutropenia requiring G-CSF; one had grade 4 thrombocytopenia and grade 2 acute hepatitis lasting ≥7 days).

The MTD was confirmed in part 2. Two of 10 patients had DLTs including grade 3 increase in ALT (recovered after 8 days) and AST (recovered after 6 days) in one patient, and grade 4 neutropenia requiring G-CSF. One patient discontinued treatment due to AEs (grade 2 thrombocytopenia and grade 3 neutropenia, both treatment related) prior to cycle 3. Seven of 10 patients received ≥3 cycles of study treatment, and ≥5 patients had at least a PR as a best overall response; therefore, investigators were instructed to proceed to part 3.

Safety and tolerability

Among 38 patients treated at the MTD, the most common treatment-related AEs of any grade were hematologic abnormalities, fatigue, liver enzyme abnormalities, and gastrointestinal toxicities; hematologic abnormalities accounted for most grade ≥3 treatment-related AEs (Table 2). Twenty-one patients treated at the MTD had reported platelet laboratory values corresponding to grade ≥3 decreased platelets, 18 of whom recovered to grade ≤1 while on study after a median of 14 (range, 6–474) days. Twenty-seven patients treated at the MTD had reported neutrophil laboratory values corresponding to grade ≥3 neutrophil count decreased, all of whom recovered to grade ≤1 after a median of 9 (3–181) days. Three patients receiving the MTD experienced treatment-related QT prolongation (grade 1, $n = 1$; grade 2, $n = 2$).

A total of 13 patients permanently discontinued treatment due to AEs, 11 of whom were treated at the MTD (Supplementary Table S2). AEs leading to discontinuation of treatment at the MTD were thrombocytopenia or delayed (>28 days) recovery from thrombocytopenia [$n = 9$ (grade 2, $n = 6$; grade 3, $n = 1$; grade 4, $n = 2$)], grade 3 neutropenia ($n = 1$; together with grade 2 thrombocytopenia), grade 2 ALT increased that prevented redosing for >28 days ($n = 1$), as well as grade 1 alkaline phosphatase and ALT increased ($n = 1$; patient had no subsequent laboratory assessments).

Six patients treated at the MTD (eight patients total) had AEs leading to dose reductions, including neutropenia ($n = 2$), leukopenia, thrombocytopenia, ALT increased, AST increased, weight decreased, and fatigue ($n = 1$ each; Supplementary

Table 2. Treatment-related AEs[a]

	Patients receiving MTD ($n = 38$)		Total ($N = 48$)	
AE, *n* (%)	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**
Any AE	38 (100)	32 (84)	48 (100)	40 (83)
Blood and lymphatic system disorders	**33 (87)**	**30 (79)**	**43 (90)**	**38 (79)**
Thrombocytopenia	31 (82)	19 (50)	40 (83)	23 (48)
Neutropenia	28 (74)	28 (74)	37 (77)	35 (73)
Leukopenia	23 (61)	18 (47)	31 (65)	21 (44)
Lymphopenia	19 (50)	16 (42)	28 (58)	22 (46)
Anemia	7 (18)	0	9 (19)	0
Gastrointestinal disorders	**28 (74)**	**2 (5)**	**37 (77)**	**2 (4)**
Constipation	16 (42)	0	23 (48)	0
Nausea	18 (47)	1 (3)	21 (44)	1 (2)
Vomiting	9 (24)	0	9 (19)	0
Stomatitis	4 (11)	0	5 (10)	0
Abdominal discomfort	4 (11)	0	4 (8)	0
Diarrhea	4 (11)	0	4 (8)	0
General disorders and admin. site conditions	**26 (68)**	**1 (3)**	**32 (67)**	**1 (2)**
Fatigue	19 (50)	1 (3)	22 (46)	1 (2)
Malaise	6 (16)	0	8 (17)	0
Pyrexia	6 (16)	0	8 (17)	0
Nervous system disorders	**23 (61)**	**0**	**30 (63)**	**0**
Peripheral neuropathy	8 (21)	0	11 (23)	0
Hypoesthesia	8 (21)	0	10 (21)	0
Dysgeusia	5 (13)	0	8 (17)	0
Investigations	**22 (58)**	**2 (5)**	**29 (60)**	**3 (6)**
AST increased	14 (37)	1 (3)	19 (40)	2 (4)
ALT increased	12 (32)	2 (5)	16 (33)	3 (6)
AP increased	8 (21)	0	12 (25)	0
LDH increased	3 (8)	0	6 (13)	0
Hepatobiliary disorders	**16 (42)**	**1 (3)**	**22 (46)**	**2 (4)**
Hyperbilirubinemia	13 (34)	1 (3)	18 (38)	2 (4)
Liver disorder	7 (18)	0	10 (21)	0
Metabolism and nutrition disorders	**16 (42)**	**1 (3)**	**22 (46)**	**1 (2)**
Decreased appetite	9 (24)	0	13 (27)	0
Hyperglycemia	5 (13)	0	8 (17)	0
Skin and subcutaneous tissue disorders	**10 (26)**	**0**	**15 (31)**	**0**
Alopecia	9 (24)	0	12 (25)	0
Musculoskeletal and connective tissue disorders	**8 (21)**	**0**	**12 (25)**	**0**
Arthralgia	3 (8)	0	5 (10)	0
Immune system disorders	**7 (18)**	**0**	**8 (17)**	**0**
Drug hypersensitivity	4 (11)	0	5 (10)	0
Psychiatric disorders	**5 (13)**	**0**	**5 (10)**	**0**
Insomnia	4 (11)	0	4 (8)	0

NOTE: Other grade ≥3 treatment-related AEs experienced by patients treated at the MTD were febrile neutropenia ($n = 2$), pneumococcal pneumonia and urosepsis ($n = 1$; same patient), leukocytosis, pneumonia, sepsis, infective arthritis, enteritis, and hyponatremia (all $n = 1$).

Abbreviations: Admin., administration; AP, alkaline phosphatase; LDH, lactate dehydrogenase.

[a]Treatment-related AEs occurring on or after the first dose date until 56 days after the last dose in ≥10% of patients treated at the MTD or in total are shown under the relevant Medical Dictionary for Regulated Activities System Organ Class (in bold) and preferred terms.

Table S2). AEs leading to dose delays occurred with 24 patients receiving the MTD (26 patients total). Of these AEs, only neutropenia and thrombocytopenia ($n = 10$ each) occurred in >2 patients.

A total of 13 deaths were reported, most commonly due to PD ($n = 9$). Only one patient died within 28 days after the last dose of study treatment (due to cardiopulmonary arrest secondary to DLBCL). There was one report of treatment-related fatal pneumonia associated with grade 4 neutropenia; other reasons for death include cardiorespiratory arrest and lung cancer ($n = 1$ each).

Efficacy

Among the 38 patients treated at the MTD, the overall response rate (ORR) was 84% [95% confidence interval (CI), 69%–94%], including nine CRs (Table 3). All patients treated at lower levels responded [dose level 1 ($n = 3$), two CRs and one PR; dose level 2 ($n = 3$), one CR and two PRs]; of the four patients treated at level 4, one had a CR. All 27 patients with indolent B-cell NHL responded, including 11 (41%) who achieved a CR. Among the 21 patients with aggressive B-cell NHL, a response was observed in 12 (57%) patients, two of whom achieved a CR. In addition, a response of CR or PR was achieved by five of eight patients who were refractory to most recent prior therapy, including two with aggressive histology lymphoma.

Kaplan–Meier estimated probabilities of PFS, OS, and DOR among all patients ($n = 48$) and those with indolent ($n = 27$) or aggressive ($n = 21$) B-cell NHL are shown in Fig. 2. A total of 28 patients experienced PFS events (PD, death, or new anticancer therapy). Among all 48 patients, the median (95% CI) PFS was 14.4 [6.9–not yet reached (NR)] months, and Kaplan–Meier estimated probability (95% CI) of PFS at 24 months was 0.38 (0.23–0.52). With 13 and 15 events, respectively, the

Table 3. Efficacy endpoints

	Indolent[a] ($n = 27$)	Aggressive[b] ($n = 21$)	MTD ($n = 38$)	Total treated ($n = 48$)
Response, *n* (%) [95% CI]				
ORR	27 (100) [87–100]	12 (57) [34–78]	32 (84) [69–94]	39 (81) [67–91]
CR	11 (41)	2 (10)	9 (24)	13 (27)
PR	16 (59)	10 (48)	23 (61)	26 (54)
SD	0	2 (10)	2 (5)	2 (4)
PD	0	6 (29)	4 (11)	6 (13)
Not assessed	0	1 (5)	0	1 (2)
Median (95% CI)[c], mo				
PFS	NR (13–NR)	4 (1–13)	14 (5–NR)	14 (7–NR)
OS	NR	25 (5–NR)	NR (25–NR)	NR
DOR	NR (11–NR)	11 (2–NR)	21 (9–NR)	18 (11–NR)
Probability of PFS, (95% CI)				
12 mo	0.74 (0.53–0.87)	0.32 (0.13–0.53)	0.57 (0.39–0.71)	0.56 (0.41–0.69)
24 mo	0.50 (0.29–0.68)	0.19 (0.05–0.40)	0.39 (0.23–0.54)	0.38 (0.23–0.52)
Probability of OS, (95% CI)				
12 mo	0.93 (0.74–0.98)	0.60 (0.36–0.78)	0.79 (0.62–0.89)	0.79 (0.64–0.88)
24 mo	0.89 (0.69–0.96)	0.55 (0.31–0.73)	0.74 (0.56–0.85)	0.74 (0.59–0.85)

Abbreviation: SD, stable disease.
[a]Indolent lymphoma includes follicular lymphoma and small lymphocytic lymphoma.
[b]Aggressive lymphoma includes DLBCL and mantle cell lymphoma.
[c]Calculated 95% CI using the generalized Brookmeyer–Crowley method.

median PFS was not reached for all patients with indolent B-cell NHL and was 4.4 (1.3–12.9) months for those with aggressive B-cell NHL. The Kaplan–Meier estimated probability (95% CI) of PFS at 24 months was 0.50 (0.29–0.68) for all patients with indolent B-cell NHL and 0.19 (0.05–0.40) for all patients with aggressive B-cell NHL.

After a median follow-up of 24.1 (range 1.3–38.1) months, 22 patients receiving the MTD had experienced PFS events. Among all 38 patients treated at the MTD, the median (95% CI) PFS was 14.4 (5.5–NR) months. The Kaplan–Meier estimated probability (95% CI) of PFS at 24 months was 0.39 (0.23–0.54; Table 3). For the 18 patients with aggressive B-cell NHL receiving the MTD, the median (95% CI) PFS was 4.4 (2.4–14.4) months, and Kaplan–Meier estimated probability (95% CI) of PFS at 24 months was 0.21 (0.06–0.44).

As of the data cutoff date (October 2, 2014), the median OS has not been reached for patients who received the MTD. The median (95% CI) OS was also not reached for patients with indolent B-cell NHL and was 24.5 (5.5–NR) months for patients with aggressive B-cell NHL. The Kaplan–Meier estimated probability (95% CI) of OS at 24 months was 0.74 (0.56–0.85) for patients receiving the MTD, 0.89 (0.69–0.96) for patients with indolent B-cell NHL, and 0.55 (0.31–0.73) for patients with aggressive B-cell NHL.

Among 32 responders treated at the MTD, the median (95% CI) DOR was 21.4 (9.2–NR) months (Table 3). Response duration was longer for patients with indolent [NR (11.2 months–NR)] versus aggressive [11.0 (1.8–NR) months] B-cell NHL.

Pharmacokinetics

Pharmacokinetic data from the start of cycle 3 were available from 23 patients treated at the MTD. Mean concentrations of inotuzumab ozogamicin and calicheamicin during cycle 3 are shown in Table 4. The concentrations of unconjugated calicheamicin were predominantly below the limit of quantification. Data for inotuzumab ozogamicin and total calicheamicin indicate that peak exposures were achieved at or near the end-of-infusion time, with high exposures minimally maintained through 24 hours. Total calicheamicin concentrations were usually detectable for approximately 1 week after dosing.

Immunogenicity testing using ELISA indicated that 5.9% (7/118) of samples in 8.5% (4/47) of patients were positive for anti-inotuzumab ozogamicin antibodies; however, these positive samples were primarily obtained before cycle 1 and were not considered related to inotuzumab ozogamicin treatment. Antibodies to inotuzumab ozogamicin were detected in two patients after inotuzumab ozogamicin treatment, neither of whom exhibited clinical symptoms attributable to the formation of anti-inotuzumab ozogamicin antibodies. No anti-rituximab antibodies were detected among 116 samples drawn from 46 patients.

Discussion

Currently, there is considerable interest in the potential for delivering targeted cytotoxic chemotherapeutic agents for the treatment of lymphomas by conjugating these agents with specific mAbs that recognize highly expressed cell surface proteins (30–32). Despite the progress in initial treatment of B-cell NHL using combinations of mAbs with chemotherapy, there remains an unmet clinical need as most adult patients with NHL relapse, and many become refractory to standard therapy. Results from *in vitro* studies suggest mAbs can sensitize lymphoma cells to chemotherapy (33, 34), and a synergistic effect was observed between rituximab and various cytotoxic agents in patients with relapsed/refractory disease (35–39). In addition, unconjugated mAbs generally have mild, nonoverlapping toxicities with most cytotoxic agents (40). We therefore assessed the safety, MTD, and preliminary efficacy of the addition of another targeted agent (inotuzumab ozogamicin) to R-CVP in patients with relapsed/refractory CD22+ B-cell NHL.

The MTD for inotuzumab ozogamicin plus R-CVP was determined to be inotuzumab ozogamicin 0.8 mg/m^2 plus standard-dose R-CVP given on a 21-day cycle; DLTs were hematologic (grade 4 neutropenia and thrombocytopenia)

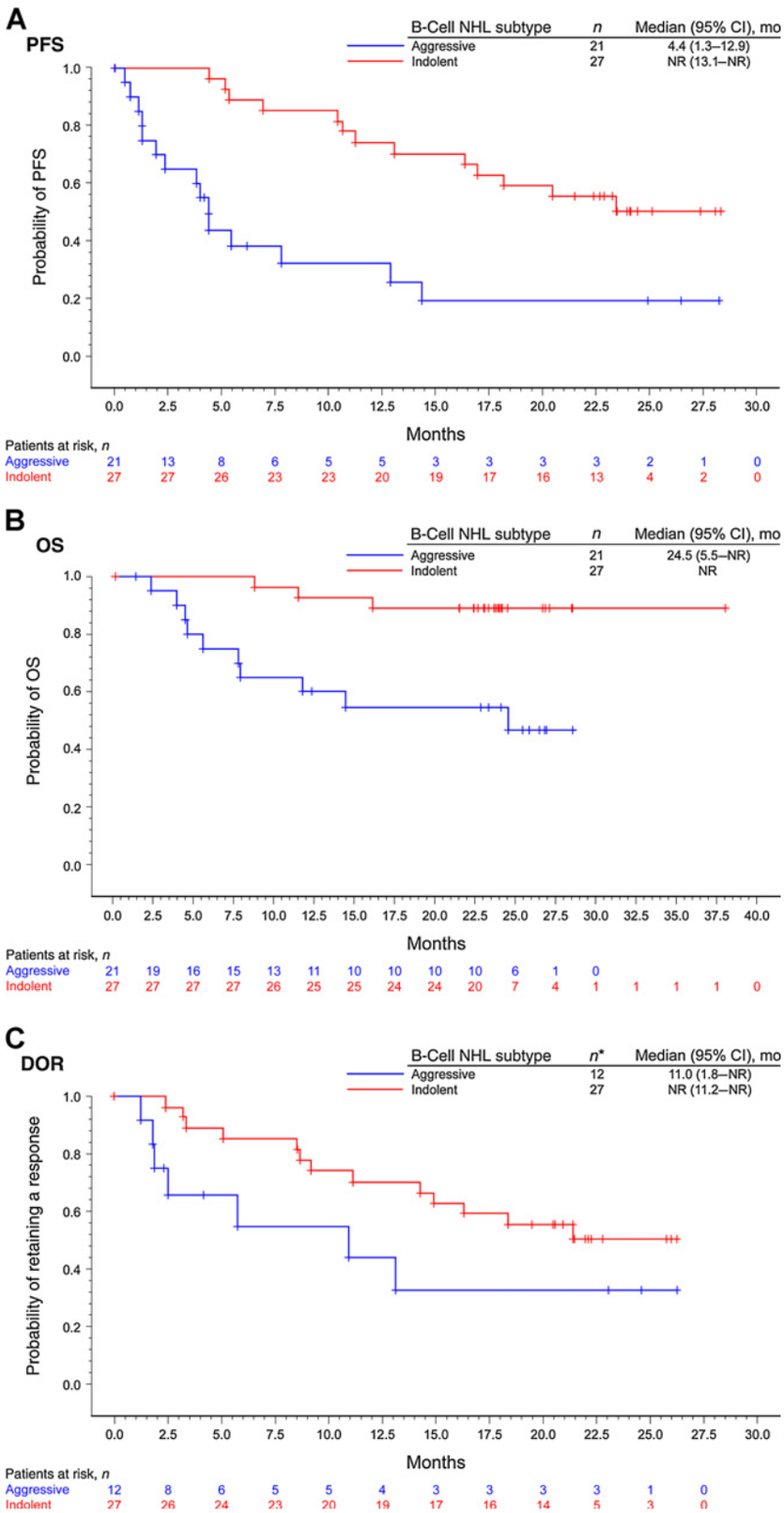

Figure 2.

Kaplan–Meier estimate of PFS (**A**), OS (**B**), and DOR (**C**). PFS was defined as the time from first dose until the first date of disease progression (including symptomatic deterioration), new antilymphoma therapy, or death from any cause. Patients without a PFS event were censored at the date of last valid postbaseline tumor assessment; patients without a PFS event and no postbaseline tumor assessment were censored at the date of first dose of study drug. OS was defined as the time from first dose to death from any cause, censoring at the last date of patient contact. DOR was defined as the time from response until the first date of disease progression (including symptomatic deterioration), new antilymphoma therapy, or death from any cause. Patients without an event were censored at the date of last valid tumor assessment. Plus (+), censored events. *, Number of responders.

Table 4. Mean concentrations of InO and total calicheamicin during cycle 3 following MTD treatment[a]

Analyte, mean (*n*, CV%)	Time, h[b]				
	0	1[c]	3	24	144
InO	—	190	214	110	—
	(23, -)	(18, 43.0)	(22, 33.5)	(22, 33.9)	(19, -)
Total calicheamicin	0	26.6	32.4	21.7	7.6
	(23, -)	(18, 27.0)	(22, 20.2)	(22, 31.0)	(19, 42.7)

Abbreviations: CV%, coefficient of variation; InO, inotuzumab ozogamicin.
[a]Concentrations expressed in units of ng/mL in serum.
[b]Elapsed time relative to start of inotuzumab ozogamicin infusion.
[c]End of inotuzumab ozogamicin infusion.

and hepatic (grade 2 hepatitis). Although dose escalation of cyclophosphamide in this combination was possible, the inotuzumab ozogamicin dose could not be increased. Consistent with the observed DLTs, toxicities associated with inotuzumab ozogamicin plus R-CVP were frequently hematologic [most commonly thrombocytopenia (83%)]; these toxicities were also the most common reason for treatment discontinuations, dose delays, and/or dose reductions. However, most patients had received $\geq$2 prior therapies, potentially predisposing them to developing hematologic AEs. Whereas fatigue (50%), constipation (42%), and nausea (47%) were the most common (any grade) treatment-related nonhematologic AEs in patients treated at the MTD, liver test abnormalities, including ALT increased (32%), AST increased (37%), and hyperbilirubinemia (34%) were also frequent and were a common reason for treatment discontinuation or dose reduction. Grade 3/4 nonhematologic AEs were uncommon. Overall, the toxicity profile of this combination was consistent with that previously reported for inotuzumab ozogamicin alone (18, 19), or in combination with rituximab (20, 21).

The benefit of adding rituximab to chemotherapeutic regimens to response and survival rates is well established (2, 3, 41–45), and immunochemotherapies have become standard treatments for relapsed/refractory disease. However, the addition of anthracyclines to CVP significantly increases the toxicity of the regimen (46, 47); R-CVP may be preferable to anthracycline-containing regimens in patients with a known cardiac history or for whom cumulative cardiac toxicity may be of concern; as such, R-CVP was chosen in this study for coadministration with inotuzumab ozogamicin.

Interpretation of the efficacy data is limited by the small sample size and heterogeneity of enrolled patients. In addition, observed responses and response durations should be interpreted in the light of the low risk of many of the patients enrolled in this study, as 13 (34%) of the 38 patients treated at the MTD had stage I/II disease at study entry and 16 (42%) had achieved a CR to their most recent prior regimen. Nevertheless, the preliminary efficacy is encouraging, with 11 and two CRs observed in patients with indolent and aggressive B-cell NHL, respectively. The ORR for all follicular lymphoma patients receiving inotuzumab ozogamicin plus R-CVP (100%) compares favorably with that reported for frontline R-CVP in patients with follicular lymphoma (81%; ref. 44) and appears similar to that reported for rituximab plus inotuzumab ozogamicin (80%) in early-phase studies (22, 23). In addition, there was a 57% response rate in patients with aggressive lymphoma. This suggests that it may be appropriate to examine inotuzumab ozogamicin in combination with R-CVP in patients unable to tolerate anthracyclines (48), and a study of this regimen in chemotherapy-naïve patients with DLBCL who are not candidates for anthracycline-based treatment is currently recruiting (49). Treatment at the MTD was also associated with notable PFS and OS rates at 24 months of 39% and 74%, respectively.

Circulating levels of inotuzumab ozogamicin, total calicheamicin, and unconjugated calicheamicin appear comparable with those previously reported following concomitant treatment of inotuzumab ozogamicin with rituximab alone in patients with B-NHL (23). The potential for the formation of anti-inotuzumab ozogamicin and anti-rituximab antibodies appears low.

In conclusion, inotuzumab ozogamicin 0.8 mg/m^2 given with standard-dose R-CVP demonstrated manageable safety and tolerability. Nearly all grade 3/4 AEs in this heavily pretreated population were hematologic, most commonly thrombocytopenia and neutropenia. Although the antitumor activity of this combination was noteworthy, further investigation in a larger population would be required to determine whether this regimen offers an advantage over other previously established regimens or whether inotuzumab ozogamicin should be combined with other agents.

Disclosure of Potential Conflicts of Interest

M. Ogura reports receiving speakers bureau honoraria from Takeda Pharmaceutical Co., Ltd., and is a consultant/advisory board member for Celgene, MeijiSeika Pharma, Mundipharma, and Sandoz. K. Tobinai reports receiving commercial research grants from Abbvie, Celgene, Chugai Pharmaceutical, Eisai, GlaxoSmithKline, Janssen Pharmaceutical, Ono Pharmaceutical, and Servier. A. Davies is a consultant/advisory board member for CTI, Gilead, Karyopharma, Mudipharma, Roche, and Takeda, reports receiving commercial research grants from Acerta, Bayer, Gilead, GlaxoSmithKline, Karyopharma, Pfizer, Roche, and Takeda, and reports receiving fees for presentation at an educational meeting from Janssen. M. Crump is a consultant/advisory board member for Celgene, Roche Canada, and Seattle Genetics. L. Paccagnella and E. Vandendries have ownership interest (including patents) in Pfizer. D. MacDonald is a consultant/advisory board member for Roche Canada.

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