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Initial Experience With CMC-544 (Inotuzumab Ozogamicin) in Pediatric Patients With Relapsed B-Cell Acute Lymphoblastic Leukemia

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Abstract

Survival is poor in pediatric patients with relapsed or refractory acute B-cell lymphoblastic leukemia (ALL) and therapeutic options are limited. CMC-544 (inotuzumab ozogamicin) has shown significant activity in adult patients with relapsed and refractory ALL. We evaluated CMC-544 in pediatric patients with multiply relapsed ALL. Five children 4–15 years old with relapsed, CD 22 positive B-cell ALL were enrolled on a phase II non-randomized trial of CMC-544. CMC-544 was initially administered at 1.3 mg/m^2 every 3 weeks. The dose then increased to 1.8 mg/m^2 every 3 weeks. Subsequently, a weekly schedule of CMC-544 given as 0.8 mg/m^2 on day 1 followed by 0.5 mg/m^2 on days 8 and 15 was administered. All five patients had refractory relapsed B-cell ALL. Lymphoblasts for all patients highly expressed CD22. Four patients had two or more relapses before starting the study drug. One patient achieved a complete remission in the bone marrow and normal peripheral counts, and two patients achieved bone marrow morphologic remission with absolute neutrophils >1,000/μl but platelets <100,000/μl. Two patients had no response to the drug. Toxicities consisted of fever, sepsis, and liver enzyme elevation. Single agent CMC-544 given at the single dose of 1.8 mg/m^2 every 3 weeks or given as a split, weekly dose was generally well tolerated considering the inherent risks in this population of patients and showed promising activity in pediatric patients with relapsed and refractory ALL

Keywords

acute lymphoblastic leukemia; CD 22; CMC-544; relapse

INTRODUCTION

Relapsed ALL, particularly early relapsed disease, is difficult to treat and cure [1–3]. Patients with early relapse, multiple relapses, relapse after BMT or with ALL that is refractory to conventional therapy have a dismal prognosis [4–6]. Unfortunately, relapsed ALL is not uncommon in pediatric hematology/oncology. Relapsed ALL patients, as a

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group, constitute the 4th most commonly encountered malignancy in pediatric hematology/oncology practice [3,7]. As with children, adults with relapsed ALL fare poorly [8,9]. New therapies that target malignant lymphoblasts are needed for patients of all ages with relapsed ALL.

CMC-544 is a monoclonal antibody drug conjugate (ADC) that targets the CD22 antigen. CD22 is present on malignant lymphoblasts in the majority of cases of B-cell ALL and, to a lesser extent, it is present on some normal lymphocytes [10,11]. CD22 is one of the best internalized cell surface proteins on lymphoblasts, and it is not shed into the circulation [7]. CMC-544 consists of a monoclonal antibody to CD22 conjugated to a synthetic derivative of calicheamicin. After internalization and release from the ADC, calicheamicin avidly binds to the minor groove of double stranded DNA and causes double stranded breaks. This results in cell death [12]. In adults with relapsed, CD22-positive non-Hodgkin's lymphoma and in adults with relapsed or refractory CD22-positive ALL, single agent CMC-544 has shown promising anti-tumor activity and an acceptable safety profile [13,14]. In a single arm phase II study, adult patients with relapsed B-cell ALL demonstrated a 57% conventional complete response or complete response minus platelet recovery [14]. The most common toxicities encountered in patients enrolled on this phase II study were grade 1 fevers and grade 1–2 transaminase elevations. Grade 1 or 2 transaminase elevations were seen in about 67% of patients, and these elevations almost all resolved. Fractionating the dose of CMC-544 into three doses given weekly that summed up to 1.8 mg/m^2 per treatment cycle of drug resulted in similar anti-leukemia activity, but there was less fever, infusion reactions, and liver toxicity. Early results in 17 adult patients on the split, weekly dosing schedule showed the combined CR/CRp/ marrow CR rate to be 8/17. Common toxicities seen in adults with B-cell ALL treated with CMC-544 include myelosuppression, with more than 50% of patients experiencing thrombocytopenia or neutropenia, transaminase elevation, fatigue and decreased appetite. Prominent grade 3 or 4 toxicities were all hematologic, as expected in this patient population. Of note, ADC conjugates that employ calicheamicin have been associated with VOD [15,16]. This toxicity is especially worrisome in this patient population since the goal of chemotherapy in the setting of relapsed ALL is to induce a remission so that the patient can proceed to a stem cell transplant.

Overall, the efficacy of single agent CMC-544 seen in adults with relapsed B-cell ALL and the acceptable toxicity profile in adult patients make CMC-544 a therapy worth evaluating in pediatric patients with relapsed B-cell ALL despite the concerns about VOD.

PATIENTS AND METHODS

Patients

Clinical data on pediatric patients younger than 18 years of age with relapsed CD22 positive ALL treated with CMC-544 were retrospectively reviewed for safety, toxicity, and response. All patients had disease that had relapsed after standard chemotherapy, and all patients were subsequently refractory to conventional chemotherapy for relapse. Patients with prior BMT were eligible. 4/5 patients had 3 or more prior chemotherapy regimens and 2/5 patients had relapsed disease post bone marrow transplant (Table I). Patient 1 relapsed 11 months post BMT, while patient 3 relapsed 6 months after his second transplant. An initial bone marrow

confirming ALL relapse was performed, and CD22 expression on lymphoblasts was determined by flow cytometry. CD22 positivity on the patient lymphoblast populations ranged from 72% to 100% (Table I). Informed written consent was obtained from the appropriate caretaker prior to starting therapy, and assent for therapy from pediatric patients age seven and above was also obtained. The inclusion of children in this trial was approved by the institutional review board (IRB).

Treatment

Initially, CMC-544 was administered as an intravenous infusion over 1 hour at 1.3 mg/m^2 once every 3 weeks. Pre-medications to prevent infusion reactions were allowed. Since CMC-544 was an investigational agent with no prior use in pediatric patients, the protocol was specifically designed so that 10 adult patients were required to be treated at the baseline dose without dose limiting toxicity before pediatric patients could start to enroll. Three of the five children were treated at the 1.3 mg/m^2 dose given once every 3 weeks. In the phase I portion of the study, the dose was eventually safely escalated in adult patients to 1.8 mg/m^2/ cycle. Subsequently, pediatric patients were eligible for enrollment at the 1.8 mg/m^2 dose level. Cycles were repeated every 21 days. Previously published *in vitro* studies of CMC-544 indicated that repeated, low-dose therapy might be superior to single, high-dose therapy with this agent [17]. Pharmacokinetic data from adult patients enrolled at the every 3-week dose schedule suggested that a lower dose given weekly might be equally effective. The protocol was then amended to evaluate a weekly dose schedule of 0.8 mg/m^2 the first week followed by 0.5 mg/m^2 in weeks 2 and 3. Once the weekly doses schedule was tested in adults and no new toxicities were observed, pediatric patients were eligible to enroll on the weekly schedule of 0.8 mg/m^2 week one, and then 0.5 mg/m^2 weekly for two doses.

Evaluation of Response

Patients were initially enrolled on CMC-544 given every 3 weeks. Bone marrow aspirations were done on day 14 and 21 of each cycle. Patients were allowed to continue on CMC for as many as eight cycles before they were taken off study. Bone marrow samples were evaluated for routine morphology. Additional marrow samples were simultaneously sent for flow cytometry evaluation, including evaluation for minimal residual disease (MRD) when indicated. A bone marrow morphological remission (mCR) was defined as less than 5% blasts in an adequately cellular sample. CR was defined as a bone marrow morphological remission accompanied by recovery of the absolute neutrophil count (ANC) to 1,000/ μl and the platelet count to 100,000/μl. Patients who recovered their ANC to 1,000/μl or greater but who did not achieve a platelet count of 100,000/μl were categorized as CR with inadequate platelet response (CRp). Patients with no response could be taken off therapy at the discretion of the treating physician, but a minimum of two cycles was recommended.

Safety Evaluation

At the start of therapy, all patients were screened for eligibility. To enroll, the creatinine was required to be 2 mg/dl or less, the bilirubin 1.5 × upper limit of normal (ULN) or less, and the AST 3 × ULN or less. A pre-treatment echocardiogram showing an ejection fraction over 45% and a normal EKG were required prior to the start of treatment. Patients with controlled infections were allowed to enroll, and there was no performance status limitation. No

pediatric patients were assessed for eligibility and deemed ineligible due to poor performance status. Premedication with acetaminophen and corticosteroids was given prior to drug infusion. Toxicity was graded according to the NCI Common Terminology Criteria for Adverse Events version 3.0.

RESULTS

Response to Treatment

Five pediatric patients aged approximately 5, 6.5, 11, 14, and 15 years of age were treated with CMC-544 on this study. Table I summarizes the patient characteristics and prior treatment regimens with previous responses to conventional chemotherapy. All patients received at least two cycles of therapy, and, in those patients who responded, the response was noted after the first cycle of treatment in two patients and after two cycles in one patient. Three patients were enrolled on CMC-544 at 1.3 mg/m^2 every 3 weeks, one of whom had a dose escalation to 1.8 mg/m^2 for the second cycle. Two patients received the weekly schedule of CMC-544 at 0.8, 0.5, and 0.5 mg/m^2/week. No patients had evidence of extramedullary leukemia at the time of enrollment. All pediatric patients were able to complete each planned cycle of chemotherapy.

Patients 3 and 4 had no response to the study drug. Patient 3 had Li-Fraumeni syndrome and had relapsed after bone marrow transplant. His bone marrow evaluation done at day 14 showed a minor decrease in blasts from 83% to 54% after the first dose of CMC-544. Patient 4 was treated on the weekly schedule. He received three cycles of therapy but had no improvement in bone marrow blast percentage.

Patients 1 and 5 achieved a CRp after one and two courses of CMC-544, respectively. Both patients had relapsed leukemia refractory to chemotherapy. Patient 1 relapsed within 22 weeks of first CR following a bone marrow transplant and then received CMC-544 as a fourth treatment for relapse. Patient 5 received CMC-544 as salvage 3 therapy. Patient 1 was treated on the 3-week 1.3 mg/m^2 dose schedule for three cycles, and patient 5 received weekly study drug at 1.8 mg/m^2 per cycle for two cycles. After treatment with CMC-544, each patient reached an ANC of over 1,500/μl and a platelet count over 50,000/μl prior to proceeding to repeat transplantation. For the responding patients, the time to best response corresponds to the number of cycles of CMC-544; patients that had responded then went to BMT. The time to response was two cycles for patients 1 and 2 and one cycle for patient 5. The duration of remission was short, as all patients who responded were taken to BMT within 4 weeks either CRp or CR.

Patient 2 had a brief initial remission with conventional treatment (13 weeks). After one course of CMC-544, the patient had 14% blasts (an earlier marrow was hypocellular with 1% blasts). After the second course, she had 1% blasts by flow cytometry and normal peripheral counts. She remained MRD positive with approximately 1% blasts detected by flow cytometry prior to bone marrow transplantation. Of the three patients that went on to BMT, two have relapsed and died. The other responding patient relapsed over 100 days after transplant and is getting further therapy.

Evaluation of Toxicity

In the five pediatric patients with relapsed ALL, CMC-544 was relatively well tolerated. A common grade 1–2 toxicity in patients of all ages is fever, which was seen in nine (20%) of adult patients. Fever was also reported in 3 out of 5 pediatric patients, all with the first infusion of the CMC-544. Hypotension during the antibody-drug infusion did not occur in these children. As in adults, Grade 3–4 toxicities were infrequent. As an example, grade 3–4 bilirubin elevation, the most common serious toxicity in adults, was seen in two (4%) of adult patients [14]. None of the five pediatric patients developed grade 3–4 hepatic toxicity. Two of the five patients did develop Gr II elevations in ALT, which resolved. Three pediatric patients proceeded to transplant following CMC-544 therapy, and one of transplanted pediatric patients developed VOD following an unrelated donor BMT. The preparative regimen for this patient was busulfan and clofarabine. The episode of VOD in this patient resolved after therapy with defibrotide. One pediatric patient died of sepsis. He was deconditioned, had a rapidly rising WBC with circulating blasts, and had been neutropenic for >6 weeks prior to starting CMC-544. One pediatric patient developed a perianal fissure during CMC-544 therapy. This patient produced a small number of neutrophils while on therapy, and he healed completely while on study therapy despite having no significant marrow response.

DISCUSSION

CMC-544 has demonstrated activity against B-cell ALL in adult patients with relapsed disease [14]. Due to the encouraging response rate in adults and the distinct mechanism of action of the drug, CMC-544 appeared to be an attractive option for pediatric patients with relapsed ALL not responding to conventional therapy. As would be predicted historically, pediatric patients tolerated the drug at least as well as their adult counterparts. Infusion reactions occurred, but were manageable. As would be expected in this severely neutropenic group, hospitalization for fever and neutropenia was occasionally necessary.

This initial pediatric experience with CMC-544 in relapsed ALL did not explore the maximum tolerated dose for pediatric patients. Rather, the treatment protocol provided experience in pediatric patients with a promising new agent at doses known to be safe in adult patients. The drug appeared to be well tolerated. Three out of five patients not responding to high-dose chemotherapy for relapsed B-cell ALL became transfusion independent and had bone marrow blasts <5% after CMC-544. The two patients with CRp had platelet counts over 50,000/μl. This warrants further evaluation. With the limited information from this initial use of CMC-544 in children, a minimum starting dose where activity can be anticipated can be postulated for a larger pediatric trial. A possible starting dose for a pediatric trial of CMC-544 would be 1.8 mg/m^2 divided into weekly infusions as this dose is well tolerated and showed activity. In addition, this pilot group provides some information on the toxicities to be expected in children following exposure to CMC-544. As noted in other trials with calicheamicin conjugate drugs (GO), the development of VOD is a possibility. Transplant preparative regimens that minimize liver toxicity may be preferred after CMC-544 therapy.

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TABLE I

Patient Characteristics and Outcomes

Patient	Age	Cytogenetic	No. of relapse prior to CMC-544	No. of treatments for current relapses (most recent)	BMT prior to CMC-544	Courses CMC-544	Response	MRD	BMT post CMC-544	Outcomes
1	6 years 7 months	46XX	3	1 (HCVAD)	Y	3	CRp	0.5%	Y	Relapsed and died post BMT
2	13 years 4 months	46XX	1	2 Ifosfamide/VP-16	N	2	CR	1%	Y (developed VOD	Relapsed and died post BMT
3	15 years 5 months	45X,-Y; Li-Fraumeni	2	0	Y (2)	2	NR	—	N	Died of sepsis
4	4 years 11 months	46XY	2	2 (clofarabine/VP-16/cyclo)	N	3	NR	—	N	Died in relapse
5	10 years 8 months	46XY, t(12;21)	2	1 (Ifosfamide/VP-16)	N	2	CRp	<0.01%	Y	Alive post relapse

MRD, minimal residual disease; BMT, bone marrow transplant; CR, complete response; NR, no response; CRp, complete response with platelets <100,000/μl; VOD, veno-occlusive disease; HCVAD, hyper cyclophosphamide, vincristine, adriamycin; cyclo, cyclophosphamide.