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Phase I/II Trial of Nanomolecular Liposomal Annamycin in Adult Patients with Relapsed/Refractory Acute Lymphoblastic Leukemia

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Abstract

Background—Treatment options for relapsed/refractory acute lymphoblastic leukemia (ALL) in adult patients remain challenging. Annamycin is a highly lipophilic form of the anthracycline doxorubicin with the ability to bypass multi-drug resistance mechanisms of cellular drug resistance.

Patients and Methods—We performed a phase I/II multi-center, open-label, study to determine the maximally tolerated dose (MTD) of nanomolecular liposomal annamycin in adult patients with refractory ALL.

Results—Thirty-one patients were enrolled; the MTD was determined to be 150 mg/m^2/day for 3 days. Other than tumor lysis syndrome, there were three grade 3 mucositis which comprised the MTD determination. There was also one case each of grade 3 diarrhea, typhlitis and nausea. After

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Authors' Contribution

Dr. Wetzler was the Principal Investigator at Roswell Park Cancer Institute, contributed to patient care, oversaw data collection and wrote the manuscript.
Dr. Thomas contributed to the care of the patients.
Dr. Wang contributed to the care of the patients.
Dr. Shepard was the Principal Investigator at Callisto.
Mrs. Ford assisted in data collection and constructed the database.
Dr. Heffner was the Principal Investigator at the Winship Cancer Institute of Emory University and contributed to the care of the patients.
Dr. Parekh was the Principal Investigator at Albert Einstein College of Medicine and contributed to the care of the patients.
Dr. Andreef contributed to the care of the patients.
Dr. O'Brien contributed to the care of the patients.
Dr. Kantarjian was the Principal Investigator at M. D. Anderson Cancer Center and contributed to the care of the patients.
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determining the MTD, a 10-patient phase IIA was conducted. Eight of the patients completed one cycle of the three days of treatment at the MTD. Of these, five (62%) had an efficacy signal with complete clearing of circulating peripheral blasts. Three of these subjects also cleared bone marrow blasts with one subsequently proceeding onto successful stem cell transplantation.

Conclusion—Single agent nanomolecular liposomal annamycin appears to be well-tolerated and evidence of clinical activity as a single agent in refractory adult ALL.

Introduction

There continues to be no effective second line therapy for refractory acute lymphoblastic leukemia (ALL) in adult patients, except nelarabine[1] and liposomal vincristine,[2] and the cure rate with current therapy has not significantly improved in decades. Since the ATP-binding cassette, subfamily B (MDR), member 1 (ABCB1) protein expression is an independent predictor of complete remission (CR) in newly diagnosed adult ALL patients,[3] developing new drugs that bypass this pathway seems rational.

Annamycin (3'-deamino-4'-epi-3'hydroxy-2'-iodo-4-demethoxydoxorubicin) is a highly lipophilic form of the anthracycline doxorubicin with the ability to bypass the ABCB1 mechanism of cellular drug resistance.[4, 5] It also has an increased affinity to liposomes to improve drug targeting to the leukemic blasts and to reduce cardiac toxicity. A phase I trial in solid tumors revealed that the dose limiting toxicity (DLT) was thrombocytopenia, and the maximally tolerated dose (MTD) was 210 mg/m^2 when administered once every three weeks.[6] The recommended dose for future trials was 190 mg/m^2. A phase II study of annamycin alone in breast cancer did not detect any clinical activity.[7]

We performed a phase I/II multi-center, open-label, study to determine the MTD of annamycin in adult patients with relapsed/refractory ALL.

Methods

Patient Eligibility

Patients with relapsed/refractory ALL 15 years or older, free of previous therapy within two weeks prior to first dose of study drug with Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 were eligible. Other eligibility criteria included adequate hepatic [bilirubin <2 the upper limit of normal (ULN) and serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT) and alkaline phosphatase <3 times the ULN] and renal (creatinine <2 times the ULN) functions; absence of uncontrolled intercurrent illnesses, including, but not limited to, infections and myocardial infarction, or other organ dysfunction (e.g., left ventricular ejection fraction >40%). All patients signed informed consent according to institutional guidelines and in compliance with the Declaration of Helsinki. The study was registered as NCT00271063.

Study Design and Treatment Plan

This study used a classical 3 + 3 phase I design. The starting annamycin dose was 190 mg/m^2/day for three consecutive days followed by 18 days off study drug (treatment cycle equaled 21 days). Provided that no patient experienced a DLT, the subsequent group of three patients was to receive the next higher liposomal annamycin dose. The next planned doses were 230, 280 and 310 mg/m^2/day. A −1 dose level was planned as 150 mg/m^2/day for three days.

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DLT and Escalation Rules

DLT was defined as study drug-related grade 3 or higher non-hematologic toxicity occurring during the first 21 days. If one of the three initial patients experienced DLT, the cohort of patients at the initial dose level was to be expanded to six patients. If at least two of the six patients experienced a DLT, then three patients would have been treated at the next lower dose level. The MTD was defined as the highest dose of liposomal annamycin at which fewer than two (of a cohort of up to six) patients experienced a DLT.

Response and Toxicity Criteria and Statistical Methods

Response criteria were achievement of CR defined as ≤5% blasts, granulocyte count of $\geq 1\times10^9$/L, and a platelet count of $\geq 100\times10^9$/L. Partial remission was defined the same as CR, except for the presence of 6% to 25% blasts. Hematologic improvement was defined as for CR but platelet count $<100\times10^9$/L. Toxicity criteria were defined using the National Cancer Institute Common Terminology Criteria for Adverse Events v 3.0. A minimum of one course (i.e., three consecutive days of treatment) was required for a subject to be included in the efficacy analysis.

Results

Patient characteristics and treatment administration

The characteristics of the 31 treated patients are listed in Table 1. Their median age was 36 (range, 19 to 77 years). A total of 16 patients underwent their initial induction with a modified Berlin-Frankfurt-Munster (BMF) regimen, either on or per Cancer and Leukemia Group B (CALGB) protocols, 12 patients underwent induction with hyper-CVAD[8] (four underwent induction with hyper-CVAD + Rituximab[9]), and three underwent other induction type regimens. Twenty-four patients achieved CR with their first induction and seven did not. The length of the first CR ranged from 0.5 to 149 months with a median of 11 months.

Initially eight patients were enrolled in the 190 mg/m^2/day dose cohort. Two of these subjects were withdrawn from the study prior to completing treatment cycle (less than 21 days) for reasons other than study drug related adverse events and were replaced. Of the six evaluable patients, two experienced a DLT (Grade 3–4 mucositis). The onset date of the Grade 3 mucositis was day 10 and the onset of Grade 4 mucositis was day 15. Therefore the 190 mg/m^2/day dose cohort was repeated to assess the whether the incidence of grade 3–4 mucositis can be reduced with the addition of Kepivance (paliformin) at a dose of 60 mcg/kg/day for three consecutive days after liposomal annamycin (days 4–6) and a prophylactic mouth wash [consisting of 4 ml diphenhydramine liquid (syrup; 12.5 mg/5 ml), 10.25 ml Maalox® and 0.75 ml viscous lidocaine (2%)]. Four additional subjects were enrolled at the 190 mg/m^2/day plus Kepivance dose cohort. Two subjects were withdrawn from the study, one due to unsatisfactory therapeutic response (a criterion on study form for withdrawal from study) and one due to an adverse event (elevated liver enzymes). A third subject experienced a DLT (grade 4 mucositis) on day 10 and was withdrawn from the study. In light of the fact that the use of Kepivance did not prevent mucositis from occurring, the study did not require the use of Kepivance prior to and after dosing with liposomal annamycin. A total of 15 patients were enrolled in the 190 mg/m^2/day dose and based on the above, the next dose was 150 mg/m^2/day. Fifteen patients were enrolled on the 150 mg/m^2/day and all received the prophylactic mouth wash but no Kepivance (one patient's annamycin dose was recorded only as the total dose).

DLT's and MTD's

The MTD was determined to be 150 mg/m^2/day for three days. Other than the tumor lysis syndrome, there were three severe adverse events (SAE) definitely related to the study drug

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consisting of grade 3 mucositis which comprised the MTD determination (Table 2). There was also one case each of grade 3 diarrhea, typhlitis and nausea. Left ventricular ejection fractions (LVEF) were unchanged after one course of treatment. Four patients received more than one course of treatment; LVEF decreased in two of them (from 50–55% to 38% in one and from 50–55% to 35% in the other) after the second course of treatment while it stayed the same in the other two patients. Two additional patients who received only one course of annamycin had late LVEF determinations that were unchanged.

Response

After determining the MTD, a 10-patient phase IIA was conducted. Eight of the patients completed one cycle of the three days of treatment at the MTD. Of these, five (62%) had an efficacy signal with complete clearing of circulating peripheral blasts. Three of these subjects also cleared bone marrow blasts with one subsequently proceeding onto successful stem cell transplantation. The other two developed tumor lysis syndrome and unfortunately expired prior to response assessment.

Discussion

A move towards liposomal drug formulations in ALL was started with the design of pegasparaginase.[10] Pegasparaginase has a prolonged half-life and is associated with decreased immunogenicity when compared to the unmodified Escherichia coli enzyme. Recent clinical trials have demonstrated its efficacy, safety and tolerability in adult ALL patients.[11, 12] Liposomal vincristine is a nanoparticle formulation of vincristine that facilitates dose-intensive treatment and was recently approved by the Food and Drug Administration for relapsed/refractory ALL.[2] Therefore, manipulating anthracyclines is a potentially effective strategy for the treatment of this aggressive malignancy. Further, since the use of anthracylines is limited by cardiotoxicity and since these agents are substrates for the drug efflux pumps, efforts to synthesize analogs with improved properties are justified. Clinical trials with different liposomal formulations of daunorubicin have been conducted[13–15] and demonstrated both efficacy and little or no cardiotoxicity. Annamycin was selected for its lack of cross resistance and a high affinity for lipid membranes.[16] Because of this latter property, annamycin is an ideal compound for liposome entrapment.

The drug was well-tolerated and showed encouraging anti-leukemic activities in the setting of poor-risk ALL. Among the eight evaluable patients at the recommended dose for phase II trial, five (62%) had evidence of anti-leukemic activity. This is remarkable considering that no other drug was approved for relapsed/refractory adult ALL since the approval of nelarabine[1] and liposomal vincristine.[2]

In conclusion, annamycin has shown a reasonable safety profile in this phase I/II study and has encouraging anti-leukemic activity. Future studies evaluating its role in combination with other anti-leukemic agents in relapsed/refractory ALL are warranted.

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Table 1

Patient Characteristics

Characteristics	Number	%
Age		
Median (years)	36	
Range	19–77	
Karyotype		
Normal	6	19%
t(9;22)	4	13%
t(v;11q23)	3	10%
Complex (≥3 aberrations)	3	10%
p16	3	10%
Other	4	13%
NA	8	26%
Lactic Dehydrogenase (IU/L)		
Median	755	
Range	145–10,000	
White blood cell count (×109/L)		
Median	3.3	
Range	<0.1 – 121.4	
Treatment Status *		
Salvage 1	6	19%
Salvage 2	8	26%
Salvage 3	6	19%
Salvage 4	6	19%
Salvage 5 or more	5	16%
ECOG Performance Status †		
0	8	27%
1	17	57%
2	5	17%

* Two patients relapsed following an allogeneic SCT prior to enrollment in the trial

† Data available on 30 patients only

Abbreviations: ECOG, Eastern Cooperative Oncology Group; NA, not available;

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Table 2

Adverse Events by grade for the (A) 190 mg/m^2 and (B) 150 mg/m^2 doses

A: Adverse Events by grade for the 190 mg/m^2 dose

Event	Gr 3(R)[SAE]	Gr 4(R)[SAE]	Gr 5(R)[SAE]
Blood/Bone Marrow			
Anemia	5(1)[0]	0	0
Increased blasts	1(0)[0]	0	1(0)[1]
Leukopenia	1(1)[0]	2(2)[1]	0
Neutropenia	0	8(0)[0]	0
Thrombocyopenia	0	13(5)[0]	0
Constitutional			
Fatigue	2(0)[0]	0	0
Weakness	2(0)[0]	0	0
Dermatology/skin			
Papulonodular lesions from fusarium on skin	1(0)[1]	0	0
Death			
Death	0	0	2(0)[1]
Gastrointestinal			
Mucositis	2(1)[1]	0	0
Nausea	1(1)[0]	0	0
Typhlitis	1(1)[1]	0	0
Hemorrhage			
Hemorrhage-posterior cerebellar	0	0	1(0)[1]
Infection			
Bacteremia	6(0)[0]	0	0
Cellulitis	1(0)[0]	0	0
Neutropenic fever	9(1)[3]	0	0
VRE stool	1(0)[0]	0	0
Metabolic			
Elevated SGOT	1(1)[0]	0	0
Hypoalbuminemia	3(0)[0]	0	0
Hypokalemia	2(0)[0]	0	0
Hyperbilirubinemia	0	1(1)[1]	0
Hyperglycemia	1(0)[0]	0	0
Hyperkalemia	1(0)[0]	0	0
Hyperphosphatemia	1(0)[0]	0	0
Hyperuricemia	1(0)[0]	0	0
Neurology			
Syncope	1(0)[0]	0	0
Ocular			

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A: Adverse Events by grade for the 190 mg/m^2 dose

Event	Gr 3(R)[SAE]	Gr 4(R)[SAE]	Gr 5(R)[SAE]
Blindness	1(0)[1]	0	0
Pulmonary			
Dyspnea	0	1(0)[0]	0
Pneumonia	3(2)[2]	0	0
Syndrome			
Tumor lysis syndrome	1(0)[1]	0	0

B: Adverse Events by grade for the 150 mg/m^2 dose

Event Gr	Gr 3(R)[SAE]	Gr 4(R)[SAE]	Gr 5(R)[SAE]
Blood/Bone Marrow			
Neutropenia	0	1(0)[1]	0
Thrombocyopenia	0	1(0)[0]	0
Cardiac			
Hypotension	1(0)[1]	0	0
Pericardial effusion	1(0)[0]	0	0
Coagulopathy			
Coagulopathy	1(0)[0]	0	0
Constitutional			
Fatigue	1(0)[0]	0	0
Weakness	1(0)[0]	0	0
Death			
Multiorgan failure	0	1(0)[1]	0
Progressive disease	0	0	2(0)[2]
Gastrointestinal			
Mucositis	1(1)[1]	0	0
Nausea	1(0)[0]	0	0
Infection			
Bacteremia	4(4)[5]	0	0
Epididymitis	1(0)[0]	0	0
Neutropenic fever	4(2)[2]	0	0
Lymphatics			
Edema-extremity	1(0)[0]	0	0
Metabolic			
Hypocalcemia	0	1(0)[0]	0
Hyperglycemia	1(0)[0]	0	0
Neurology			
Short term memory impairment	1(0)[0]	0	0
Pulmonary			
Pneumonia	1(0)[0]	0	0

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B: Adverse Events by grade for the 150 mg/m^2 dose

Event Gr	Gr 3(R)[SAE]	Gr 4(R)[SAE]	Gr 5(R)[SAE]
Syndrome			
Tumor lysis syndrome	0	0	1(1)[1]

Abbreviations: Gr, grade; R, related; SAE, serious adverse event;