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Phase 1 Study of XL119, a Rebeccamycin Analog, in Patients With Refractory Hematologic Malignancies

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Abstract

BACKGROUND—XL119 is a water-soluble derivative of rebeccamycin with dose-dependent myelosuppression as dose-limiting toxicity in phase 1 studies of solid tumors. A phase 1 study was conducted to determine the maximum tolerated dose and toxicities of XL119 in patients with advanced myelodysplastic syndrome and relapsed or refractory acute leukemias.

METHODS—Thirty-one patients were treated at 7 dose levels ranging from 140 to 260 mg/m²/daily times 5 in a 21-day cycle. Consenting patients had correlative biologic parameters studied.

RESULTS—Dose-limiting toxicity was grade 3/4 mucositis. The recommended phase 2 dose in hematologic malignancies is 240 mg/m²/daily times 5 in a 21-day cycle. Clinically significant reduction in bone marrow blasts were seen in 5 patients and additional patients had reductions in peripheral blood blasts. However, the responses were transient. Changes of plasma vascular endothelial growth factor levels from Day 1 to Day 7 correlated negatively with changes in peripheral blood blasts from Day 1 to Day 7.

CONCLUSIONS—Further assessment of XL119 in combination with other agents in patients with acute leukemias and high-risk myelodysplastic syndrome is warranted.

Keywords

XL119; rebeccamycin analog; leukemia; phase 1

Rebeccamycin is an antitumor antibiotic produced by the actinomycete *Saccharotrix aerocolonigenes*. Rebeccamycin has activity against topoisomerase I by stabilizing the topoisomerase-DNA covalent complex.¹⁻⁴ Rebeccamycin is also capable of intercalating DNA in absence of topoisomerase I. Because of the insolubility of rebeccamycin, semisynthetic and water-soluble derivatives of rebeccamycin have been created. XL119 (NSC 655,649) is such a compound that is different from rebeccamycin in its mechanism of action. In contrast to rebeccamycin, XL119 has no activity against topoisomerase I but strongly inhibits topoisomerase II.⁵ In contrast to topoisomerase II inhibition by both etoposide and teniposide, which stabilize cleaved DNA by inhibiting religation of the cleaved DNA strands, XL119 inhibits the catalytic step necessary for the passage of the intact DNA strand through the single-strand DNA break. This action leads to the formation of single, rather than double, DNA strand breaks.

XL119 has antitumor activity against P388 leukemia, melanoma, reticulum cell sarcoma, lung and colon carcinoma cell lines, and solid tumor specimens obtained from children.^{6,7} Against etoposide resistant cell lines A 549 and HCT 116, the IC₅₀ of XL119 has been 0.03 and 0.19 μ M, respectively.⁸ Keeping in line with its better solubility, XL119 is more active than rebeccamycin in intraperitoneally implanted P388 murine leukemia model, confirming its distal site activity. Plasma concentrations achieved in prior phase 1 studies using an intravenous schedule have been consistently higher than the concentrations (range, 0.03–0.21 μ g/mL) required for in vitro inhibition of topoisomerase II levels.⁹

Two phase 1 trials of XL119 in nonhematologic malignancies have explored different dosing schedules. In one, XL119 was given as a single dose every 3 weeks¹⁰ and the other study⁹ explored a dose schedule of 5 consecutive days every 3 weeks. Dose-dependent myelosuppression has been the dose-limiting toxicity (DLT) in both studies with minimal grade 3/4 nonhematologic toxicity. A third 2-step phase 1 study examined both the single-dose and multiple-dose format and has reported similar toxicities.¹¹ Because XL119 has shown preclinical antileukemia activity in an intraperitoneally implanted leukemia model, topoisomerase II inhibitors have activity in hematologic malignancies and the putative mechanism of action differs from epipodophyllotoxins, a phase 1 study of XL119 in relapsed/refractory hematologic malignancies was initiated.

Increased angiogenesis as evidenced by increased microvessel density in the bone marrow is seen in acute myelogenous leukemia (AML) and myelodysplastic syndromes (MDS).¹² Levels of plasma vascular endothelial growth factor (VEGF), a surrogate marker for angiogenesis, have prognostic implications in AML.^{13,14} Thus, monitoring of VEGF levels during therapy of leukemias may have a potential for pharmacodynamic evaluation of activity of investigational agents. Most chemotherapeutic agents induce cell death by activating the mitochondrial pathway of apoptosis.¹⁵ Activation of terminal caspases like caspase-3 is the convergence point for different pathways of apoptosis. Thus, plasma caspase-3 activity can potentially provide pharmacodynamic information regarding induction of apoptosis by therapeutic agents.

Herein we report the first phase 1 study of XL119 in hematologic malignancies. Because preclinical modeling suggested schedule dependency for this agent and no significant

nonhematologic toxicity was noted with a 5-day schedule as compared with a 1-day schedule, daily times 5 days every 21 days was the schedule selected for this study. The results of correlative studies are also reported.

MATERIALS AND METHODS

Eligibility

Patients with relapsed or refractory hematologic malignancies (AML, acute lymphoid leukemia [ALL], MDS, chronic myelogenous leukemia [CML] in blastic phase) were eligible. Eligibility criteria included 1) Eastern Cooperative Oncology Group performance status 2; 2) age 18 years or older; 3) adequate hepatic function (serum bilirubin, aspartate aminotransferase [AST], alanine aminotransferase [ALT], and creatinine upper limit of normal); and 4) no chemotherapy except hydroxyurea within 7 days of study drug treatment. All patients gave informed consent according to federal and institutional guidelines.

Drug Administration

XL119 was supplied by the National Cancer Institute (NCI) as a sterile vial containing 20 mL of a solution of 10 mg/mL of rebeccamycin analog and 1 equivalent (2.24 mg/mL) of L-tartaric acid in sterile water for injection. XL119 was given intravenously through a central venous catheter (CVC) over 60 minutes daily for 5 consecutive days. Cycles were repeated every 3 weeks. The first dose level was 140 mg/m². The dose/schedule was based on the maximum tolerated dose (MTD) and DLTs found on solid tumor phase 1 and 2 studies.

All patients who received therapy on study were considered evaluable for toxicity. Patients were evaluated on the day of therapy and at least weekly (more often if clinically indicated) while on study. At each evaluation patients were assessed for toxicity and complete blood count with platelets and differential, serum chemistries, liver function tests, and serial electrocardiograms were obtained.

Planned dose levels were 140, 160, 180, 200, 220, 240, 260 mg/m²/daily times 5 and dose escalations were carried out in a standard “3 + 3” design. Occurrence of a DLT in any patient was cause for the addition of at least 3 additional patients at that dose level. DLT was defined as a clinically significant adverse event (except nausea and vomiting) or abnormal laboratory value (nonhematologic) assessed as unrelated to disease progression, intercurrent illness, or concomitant medications and occurring during the first 21 days on study that meets any of the following criteria:

- Revised NCI Common Terminology Criteria for Adverse Events (CTCAE) (v. 3.0), grade 3 AST or ALT elevation for 7 days or grade 4 AST or ALT elevation of any duration.
- All other clinically significant toxicities that are CTCAE grade 3 or 4.
- Prolonged myelosuppression, as defined by the NCI criteria specific for leukemia, eg, marrow cellularity <5% on Day 42 or later from the start of therapy without evidence of leukemia.

The MTD was defined as the highest dose at which fewer than 2 of 6 patients experienced DLT. Patients with any response including clearance of marrow blasts were eligible to receive additional cycles. Persistent grade 2 nonhematologic toxicity required dose reduction in subsequent cycles.

Evaluation of response was done according to the modified International Working Group (IWG) criteria¹⁶ at the end of each cycle of treatment. Briefly, a complete response (CR) required disappearance of all signs and symptoms related to disease, normalization of the peripheral counts (absolute neutrophil count of $1 \times 10^9/L$ and platelet count of $100 \times 10^9/L$), and a normal bone marrow morphology with no evidence of dysplasia and 5% or fewer blasts. A partial response was defined as fulfilling the criteria for CR in the peripheral blood but with 6% to 25% abnormal cells in the marrow or 50% decrease in bone marrow blasts compared with pretreatment values. CRp was defined as per CR but with a platelet count of $<100 \times 10^9/L$.

Measurement of Caspase-3 Activity

Peripheral blood mononuclear cell caspase-3 activity was measured using a tetrapeptide Ac-DEVD-pNA (Calbiochem, San Diego, Calif) according to the manufacturer's instructions with 50 μg of cellular protein extracts. Optical densities were plotted as a function of time and the slope of the initial linear portion of the curve was used as a measurement of the amount of caspase-3 activity. The mean caspase-3 activity of peripheral blood mononuclear cells from normal controls was assigned a value of 1. The activity in the leukemic and MDS samples was normalized to the mean of controls.

Measurement of Plasma VEGF

Plasma VEGF levels were measured using a quantitative sandwich enzyme linked immunoassay (Quantikine; R&D Systems, Minneapolis, Minn) according to the manufacturer's instructions. Briefly, 100 μL of plasma was added to VEGF microplate wells and after incubation and washes a polyclonal antibody to VEGF conjugated to horseradish peroxidase was added to the wells. Color was developed by adding tetramethylbenzene as chromogen. Appropriate standards were incorporated.

Statistical Analysis

A Spearman correlation was used to analyze any possible relation of changes in peripheral blood parameters with plasma caspase activity and VEGF levels on Days 1, 7, 21, and 28.

RESULTS

Patient Characteristics

Thirty-one patients (median age, 58 years; range, 19–82 years) were enrolled. Three, 5, 3, 6, 3, 9, and 2 patients were enrolled to dose levels of 140, 160, 180, 200, 220, 240, and 260 $mg/m^2/d$, respectively. Two patients at the 160-mg dose level were replaced; 1 for receiving concomitant white cell transfusions and the other was taken off study because of a rapid increase in peripheral blood blast count. Three more patients were added to the previous cohort of 6 patients at the 240-mg dose level after encountering DLT at the 260-mg dose

level. Diagnoses included: AML (n = 25), MDS (n = 1), and ALL (n = 5). Nine of the 25 AML patients had secondary AML and all but 1 had refractory disease. One patient with AML was in second relapse after second remission of 4 months. The patient with MDS was of high-risk category (International Prognostic Scoring System = 1.5) and had undergone 4 prior therapies. All patients with ALL had prior therapy and were of pre-B origin. None of the patients with ALL had 11q23 abnormality. For all patients the median number of prior therapies was 3 (range, 0–10). The characteristics of the patients enrolled are outlined in Table 1.

Toxicity

Nonhematologic grade 1/2 toxicities are summarized in Table 2 and grade 3/4 nonhematologic toxicities are listed in Table 3. Fatigue (20%) was the most common nondose-limiting grade 3/4 nonhematologic toxicity. Transient grade 3/4 elevations of AST (13%) and bilirubin (16%) were the most frequent nonhematologic laboratory abnormalities encountered.

Four patients died while on study: 1 from sepsis, 1 from multisystem organ failure, 1 from progressive pulmonary insufficiency due to worsening of lung infiltrates that were present before study participation, and 1 from polymicrobial pneumonia and acute renal failure. Grade 2 elevation of creatinine was the most common grade 1/2 toxicity attributable to the study drug.

One patient at the 200-mg/m² dose level experienced DLTs in the form of grade 3 hand-foot syndrome and grade 4 mucositis. An expansion of this cohort yielded no further incidence of DLT. One patient at the 240-mg/m² dose level experienced DLT in the form of grade 3 mucositis. Expansion of this cohort also did not yield any further incidence of DLT. Two patients at a dose level of 260 mg/m² experienced grade 3 mucositis. Three additional patients were treated at the next-lower dose level of 240 mg/m² without encountering any DLT and this dose level was declared the MTD.

At the 220-mg/m²/d dose level, 1 patient experienced a transient grade 3 hypotension that was attributed to study medication. This hypotension was not considered a DLT and no DLT was encountered at this dose level. Also at the 240-mg/m² dose level, 1 patient was noted to have grade 3 tumor lysis syndrome, but this was not considered a DLT.

Infectious Complications—Fifteen episodes of microbiologically documented infections were encountered; 13 were bacteremic episodes, 1 polymicrobial pneumonia, and 1 *Candida fungemia*. *E. coli* and coagulase-negative *Staphylococcus* were the most frequent isolates (4 each) followed by alpha-hemolytic streptococcus (2), *Pseudomonas aeruginosa* (1), *Acinetobacter* (1), and *Enterococcus cloacae* (1). Causative agents for the episode of pneumonia included *Stenotrophomonas multophila*, coagulase-negative *Staphylococcus*, and *Klebsiella pneumoniae*.

Responses

Three patients with refractory AML achieved a significant elimination of marrow blasts (Figs. 1, 2). Because of this they received a second cycle. However their disease reappeared

soon after. The first patient at the 140-mg/m² dose level had reduction of bone marrow blast percentage from 38 to 14 by Day 28, cycle 1. At the end of the second cycle, however, the bone marrow blast percentage increased to 47 and patient was taken off-study. The second patient at the 200-mg/m² dose level had a decrease of bone marrow blasts from 31% to 21% at the end of cycle 1, but had an increase in the bone marrow blasts to 48% after the second cycle. The third patient had received 6 prior therapies and at the 260-mg/m² dose level developed grade 3 mucositis on Day 15 and was admitted to an outside facility. On his return to the M. D. Anderson Cancer Center his mucositis had resolved to grade 1 and his bone marrow blasts went from 73% to 20% on Day 38, his peripheral blood blasts went down from 53% to 0% by Day 13. Because of the clinical benefit he received a second cycle of therapy with XL119 at a reduced dose level of 240 mg/m². Unfortunately, this patient developed recurrent grade 3 mucositis and peripheral blood blasts that went back on cycle 2 Day 24 to 61%.

Two additional patients, 1 with relapsed/refractory AML (inversion 16 cytogenetics) and the other with refractory Philadelphia chromosome-positive ALL, had reductions in bone marrow blasts. In the patient with AML, bone marrow blasts went down from 89% to 32% but at the end of cycle 1 this patient developed central nervous system leukemia and decided not to pursue any further therapy. The patient with ALL had reduction in the bone marrow blasts from 93% to 0% and peripheral blood blasts from 75% to 0% but developed *E. coli* bacteremia and invasive fungal infection of the maxillary sinus and became too debilitated to be considered for any further therapy. In addition, a significant number of patients had transient reductions in their peripheral blood blasts or cleared their peripheral blood blasts (Fig. 3).

Correlative Biological Studies

Paired samples for Day 1 and Day 7 plasma VEGF levels were available for 20 patients. A strong correlation was seen between changes in peripheral blood blast percentage from Day 1 to Day 7 and changes in plasma VEGF levels on corresponding days ($R = -0.72$, $P = .0002$) (Fig. 4D). No correlation was observed between peripheral blood parameters and caspase-3 activity, VEGF levels at other timepoints.

DISCUSSION

On the basis of our study, the recommended phase 2 dose for XL119 in hematologic malignancies is 240 mg/m² daily for 5 days (through a central vein) in a 21-day cycle. This dose level is significantly higher than the 141 mg/m² (patients with prior therapy) and 175 mg/m² (patients with no prior therapy) for 5 days dose level determined in a phase 1 study conducted in patients with solid tumors.⁹ Although myelosuppression was the DLT in solid tumors, this was a desired effect in the current study in patients with refractory/relapsed hematologic malignancies. The grade 1/2 phlebitis encountered in phase 1 studies with solid tumors was not observed in our study, possibly because of central venous administration and larger volume of dilution.

Whereas DLT in the form of grade 3/4 mucositis was occasionally encountered at doses lower than the MTD, responses in the form of clearance of peripheral blood blasts and

reductions in bone marrow blasts were seen at all dose levels. These reductions in blasts were achieved rapidly. Because of the cytotoxic activity and the tolerability at lower doses, further study of XL119, perhaps in combination with other chemotherapeutic agents or targeted agents, is warranted in patients with relapsed/refractory hematologic malignancies. The experiences in studies in patients with solid tumors indicate that DLTs are commensurate with extent of prior therapies. Although the occurrence of DLT in our study population did not correlate with the number of prior therapies ($P = .5$), the median number of prior therapies in our study patients was 3 and it is quite conceivable that the occurrence of dose-limiting mucositis will be less frequent in a less heavily pretreated population.

XL119 showed antileukemic effects at multiple dose levels. Although no CR, CRp, or PRs were observed, there was a significant reduction of bone marrow and peripheral blood blasts in multiple patients. Considering the finding that most of these patients had multiple prior therapies, such activity is promising.

We expected that treatment with XL119 would induce apoptosis in leukemic blasts and activate caspase-3. Correlative studies did not reveal any difference in plasma caspase-3 levels before and after treatment with XL119. One possible explanation for this is that the mechanism of action of XL119 may be nonapoptotic cell death. A more likely possibility is that caspase-3 activation may be occurring very early and the Day 7 may be too late a timepoint for caspase-3 activity study.

Conversely, the change in peripheral blood blast count from Day 1 to Day 7 correlated with a change in plasma VEGF levels from Day 1 to Day 7. AML blasts constitutively secrete VEGF and a smaller percentage of AML cells have VEGF receptor 2 (VEGFR-2).¹⁷ VEGF can potentially act in an autocrine or paracrine fashion to enhance growth of AML cells. VEGF can also induce heat shock protein 90 (HSP-90), and HSP-90 in turn induces expression of Bcl-2 to impart apoptosis resistance to AML cells.¹⁸ Plasma levels of soluble VEGF is significantly higher in AML patients at diagnosis, compared with at remission.¹⁹ Our published work also demonstrated a correlation between plasma angiogenic factors and leukemia outcome.²⁰ The correlation between change in peripheral blood blasts and VEGF levels indicates biological activity of XL119 against leukemic blasts. The lack of correlation between blast percentage at later timepoints and VEGF levels may be a function of the refractory nature of AML blasts and their multiple mechanisms of developing rapid resistance.

In conclusion, XL119 has antileukemia activity with a DLT of mucositis. Combination studies with traditional chemotherapeutic agents as well as biologic agents like anti-VEGF agents, etc, are warranted as are studies in a less heavily pretreated population.

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FIGURE 1.
Changes in bone marrow blasts in patients receiving more than 1 cycle of XL119.

FIGURE 2.

(A) Pretreatment bone marrow biopsy (Patient 30) showing diffuse infiltration by immature blasts. (B) Day 28 bone marrow with reduction in marrow blasts.

FIGURE 3.
Changes in absolute peripheral blood blast counts in all study patients.

FIGURE 4.

Spearman correlation between changes of peripheral blood white cell count and blast percentage from Day 1 to Day 7 with peripheral blood mononuclear cell caspase-3 activity, plasma VEGF levels.

TABLE 1**Patient Characteristics**

Parameters	Median no.	No. (%)
Diagnosis		
AML	—	25 (81)
MDS	—	1 (3)
ALL	—	5 (16)
Age, y, median [range]	58 [19–82]	—
Sex		
Men	—	21 (68)
Women	—	10 (32)
Prior therapy, median [range]	3 [1–10]	—
ECOG performance status		
0–1	—	27 (87)
2	—	4 (13)
Cytogenetics		
Inv 16	—	2 (6)
Diploid	—	5 (16)
Miscellaneous	—	13 (42)
–5 to –7	—	9 (30)
Insufficient metaphases	—	2 (6)

AML indicates acute myelogenous leukemia; MDS, myelodysplastic syndrome; ALL, acute lymphoid leukemia; ECOG, European Cooperative Oncology Group.

TABLE 2

Grade 1 and 2 Toxicities in Cycle 1 by Dose Level

Dose level, mg/m ²	Total in cohort No. of patients	Parameter	
		Creatinine	Mucositis
140	3	0	0
160	5	0	0
180	3	0	0
200	6	1	0
220	3	0	0
240	9	2	1
260	2	2	0

TABLE 3

Grade 3 and 4 Toxicities in Cycle 1

Dose level, mg/m ²	No. of patients in cohort	Toxicities				
		Hand-Foot	Mucositis	MOF	Hypotension	TLS
140	3					
160	5					
180	3					
200	6	1 ^{*/†}	1 ^{*/†}	1 [*]		
220	3					
240	9		1 ^{*/†}		1	1 [*]
260	2		2 [†]			

MOF indicates multiorgan failure; TLS, tumor lysis syndrome.

* All toxicities were in the same patient.

† Dose-limiting toxicity.