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A Phase 1 Trial Dose Escalation Study of Tipifarnib on a Week-On, Week-Off Schedule in Relapsed, Refractory or High-Risk Myeloid Leukemia

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Abstract

Inhibition of farnesyltransferase (FT) activity has been associated with *in vitro* and *in vivo* anti-leukemia activity. We report the results of a phase 1 dose escalation study of tipifarnib, an oral FT inhibitor, in patients with relapsed, refractory, or newly diagnosed (if over age 70) acute myelogenous leukemia (AML), on a week-on, week-off schedule. Forty-four patients were enrolled, 2 patients were newly diagnosed, the rest were relapsed or refractory to previous treatment, with a median age of 61 (range 33–79). The maximum tolerated dose was determined to be 1200 mg given orally twice-daily (bid) on this schedule. Cycle one dose-limiting toxicities were hepatic and renal. There were 3 complete remissions seen, 2 at the 1200 mg bid dose and one at the 1000 mg bid dose, with minor responses seen at the 1400 mg bid dose level. Pharmacokinetic studies performed at doses of 1400 mg bid showed linear behavior with minimal accumulation between days 1–5. Tipifarnib administered on a week-on week-off schedule shows activity at higher doses, and represents an option for future clinical trials in AML.

Keywords

farnesyltransferase; tipifarnib; Zarnestra®; AML; acute myelogenous leukemia; phase 1 trial

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Introduction

Inhibition of farnesyltransferase activity has been associated with activity against leukemias *in vitro* and *in vivo*. Farnesylation is essential to proper functioning of ras (1), a key protein in various signaling pathways. After farnesylation, ras localizes at the plasma membrane, where it acts as a molecular switch in response to various tyrosine kinase and other cell surface receptors. Initially, ras was identified as a potential target in myeloid malignancies due to the frequency of N-ras mutations in acute myelogenous leukemia and myelodysplasia. However, clinical trials thus far have shown activity for farnesyltransferase inhibitors (FTI) even in the absence of *RAS* mutation (2), suggesting that interference with unmutated ras is itself an effective antineoplastic approach, and/or that other farnesylated proteins, such as rhoB or the lamins may also be inhibited (3). As there are over 1000 farnesylated proteins, it remains unclear which are targeted by FTIs, and which are clinically relevant. Inhibition of farnesylation on specific proteins may differ depending on the dosing and schedule of the FTI inhibitor.

Tipifarnib (R115777, Zarnestra®) is a methylquinolone analogue that competes with the CAAX motif for farnesylation. The initial phase1 trial, R115777-USA-1, conducted at the National Cancer Institute, used a 5-day, every 12 hour, dosing regimen with an intra-patient and inter-patient dose-escalation scheme (4). Protocol-defined maximum tolerated dose (MTD) was not achieved at the highest dose level (1300 mg twice daily for five days).

Tipifarnib was studied in myeloid and lymphoid leukemias by Karp, *et al*. (2), with a dose escalation built upon a 21-day continuous dosing schedule. A 29% overall response rate was noted in 34 patients, including a CR at the lowest dose level (100 mg bid). In a follow-up phase 2 study, dosing at 600 mg twice daily (bid) using the same 21 day schedule, in older patients with previously untreated AML or MDS, CR was observed in 14% of patients, with an additional 10% showing partial response (5). A study at M.D. Anderson, for patients with MDS, also using the 21-day bid dosing schedule, demonstrated a 30% response rate in 20 patients (6). Their MTD was 400 mg bid; above that dose there were several dose limiting toxicities including headache, fatigue, confusion, and vision changes.

It is conceivable that altering the dosing schedule so that tipifarnib is given in a week-on, week-off schedule may allow tolerance of administration at higher dose. In a California Cancer Consortium solid tumor phase 1 study of week-on, week-off dosing, a DLT of grade 3 fatigue occurred at the 900 mg bid dose level; no other significant grade 3 toxicities were noted (7). In hematologic malignancies, a trial of tipifarnib given on a week-on, week-off schedule in patients with high grade myelodysplastic syndrome showed reasonable tolerability and responses at different dose levels. Importantly, correlative studies performed during this trial and others, have demonstrated farnesyl transferase inhibition for seven days after administration of tipifarnib (6–8), suggesting that this alternate-week dosing schedule is mechanistically appropriate , and that dose escalation on this schedule might enhance the activity of tipifarnib in relapsed, refractory AML.

Thus, we propose a study of this dose escalation regimen in acute myeloid malignancies. Pharmacokinetic studies were done to determine the effect of dose on blood levels. Should

this regimen be equally effective as conventional-dose tipifarnib monotherapy, but with better tolerability and advantageous pKs, it could serve as a platform for combination with other agents and chemotherapies.

PATIENTS AND METHODS

Patient Selection

Eligible patients were age 18 or over with acute myeloid leukemia (AML) including: relapsed or refractory disease after one to three prior induction regimens (not counting consolidation therapies while in CR, such as autologous transplant), newly diagnosed disease in patients up to age-70 with poor risk features (unfavorable cytogenetics or findings suggestive of prior myelodysplasia) not fit for standard induction therapy, and newly diagnosed AML patients age 70 – 75 not fit for standard therapy (without history of prior MDS). Patients with acute promyelocytic leukemia of the M3 subtype were excluded. Bone marrow and peripheral blood studies were required for confirmation of diagnosis. Patients who had been treated with prior autologous transplant, were eligible, and patients post allogeneic transplant were allowed in the expansion cohort as long as there was no active graft versus host disease or infectious disease related to transplant. A minimum of 4 weeks must have elapsed since completion of prior chemotherapy in order to be eligible. Standard end organ function criteria were applied, such as serum bilirubin ≤2.0 mg/dl, SGOT and SGPT ≤2.5 times the institutional upper limits of normal and excluding patients with a pretreatment calculated creatinine clearance (absolute value) of less than 60 ml/minute or serum creatinine of < 1.5 × upper limit of normal. There were no minimum hematological parameter requirements prior to enrollment, as patients with AML and MDS are understood to have low ANC and platelet counts when the disease is active. However, patients with WBC greater than 30,000 received hydroxyurea to reduce WBC to below 30,000 at which point they were able to commence therapy. Signed informed consent was obtained for all study participants and registered by the Data Coordinating Center at City of Hope. Protocol and consent forms were approved by the institutional review boards of the participating centers.

Treatment Plan

Oral tipifarnib was administered twice daily on days 1–7 and days 15–21 of each 28-day cycle. The planned dosing levels are presented in Table 1. Patients received a minimum of one treatment cycle, with no pre-defined maximum number of cycles. Patients were permitted to stay on study as long as there were no unacceptable toxicities. Intra-patient dose escalation was permitted (not beyond the highest dose tested) if CR was not reached in the first cycle and there was no significant toxicity. At the higher dose levels, intravenous hydration was frequently given with the morning tipifarnib dose. For subjects with rapidly rising white blood cell counts after week 1 or 3 of any cycle, hydroxyurea was permitted on the intervening week until 24 hours prior to restarting the next dose of tipifarnib. Allopurinol was started 24 hours before the first dose of tipifarnib and continued until at least day 22 of the first cycle.

Evaluation of response

Bone marrow aspiration and biopsies were performed as part of the on-study evaluation within two weeks prior to starting therapy. Patients were seen a minimum of once weekly while on study, with peripheral blood counts and chemistry monitored at least once weekly. Bone marrow studies were repeated between days 26 to 28 of each cycle. Clinical responses were measured according to International Working Group criteria (9).

Study Design

Patients were enrolled in cohorts of 3, as per standard 3+3 phase 1 study design. Patients completed study diaries which were reviewed as part of the toxicity assessment at each clinic visit. Adverse events (AEs) were graded using the NCI common toxicity criteria (CTCAE) version 3.0. Dose limiting toxicities (DLT) were defined as any grade 2 to 4 non-hematologic toxicity possibly related to study drug, except for nausea, vomiting and diarrhea controllable by routine palliation, any electrolyte disturbance corrected with supplementation, or any grade 4 hematologic toxicity in the absence of circulating blasts not reversible to grade 3 or less, by 21 days after the end of a cycle. In the presence of residual leukemia seen upon aspiration, neutropenia and thrombocytopenia did not count as DLT. Dose escalation proceeded if none of the 3 patients in the cohort had a first cycle DLT. If one of the three patients in a cohort experienced a DLT, three more patients were accrued at that dose level. In the event that a second patient experienced a DLT, that is, 2 or more out of 6 patients, then patients were accrued to the next lower dose level. The maximally tolerated dose (MTD) was defined as that at which no more than one patient out of six experienced a DLT during the first cycle of treatment. Intra-patient dose escalation to highest dose open for accrual was allowed if CR was not reached in the first cycle. If PR or clinical improvement was not reached after 6 cycles, patients were categorized as treatment failure and removed from the study.

Pharmacokinetic studies

Venous blood samples were collected in heparinized tubes at the following times during the first cycle: prior to the dose on Day 1, and then at 0.5, 1, 2, 3, 5, 8 and 12 hours post dosing, and immediately before the dose on Day 5, and then at 0.5, 1, 2, 3, 5, 8 and 12 hours post dosing. Blood was centrifuged for 10 minutes at 1000 × g within 2 hours after collection for separation of plasma, and the resulting plasma samples were stored frozen at < -20°C until batch analysis. Plasma concentrations of tipifarnib were determined using a previously described validated LCMS/MS assay (10).

Individual plasma concentration-time data were analyzed using standard non-compartmental methods and the following pharmacokinetic parameters of tipifanib were determined for each patient around doses on Days 1 and 5: peak plasma concentration (C_{max}), time to reach the peak plasma concentration (T_{max}), area under the plasma concentration-time curve from 0 to 12 hours post-dosing (AUC_{12h})., and the trough plasma concentration (C_{min}). In addition, the accumulation index was determined by dividing the AUC_{12h} on Day 5 by the AUC_{12h} determined on Day 1.

Results

A total of 44 eligible patients with AML were enrolled in the study. Demographic data are listed in Table 1. Median age was 61 (range 33–79). Two patients were newly diagnosed; the remaining 42 had relapsed or failed prior therapy, including 5 patients with prior autologous transplant and 2 patients with prior allogeneic transplant.

Toxicity

At the 400 mg bid dose level, a grade 5 hepatorenal failure occurred, potentially related to the study drug. There were no additional DLTs, and no DLTs at 600 mg bid, 800 mg bid or 1000 mg bid. At the 1200 mg bid dose level, a grade 3 elevation of the creatinine was seen in one patient out of 6 treated. At the 1400 mg bid dose level, in an expanded cohort during dose de-escalation one patient experienced a grade 4 hypotension and a rising grade 2 creatinine that were dose limiting, and a second patient had a rising grade 2 creatinine in cycle 1, where treatment was terminated before it reached a grade 3 and was therefore considered dose limiting. At the 1600 mg dose level, a grade 3 LFT and a rising grade 2 creatinine, were dose limiting, and in a second patient, a rapidly rising creatinine was seen and the drug stopped before grade 3 was reached. As result, the 1200 mg bid dose was established as the maximum tolerated dose (MTD) and an additional 7 patients were treated at the MTD. In the total of 13 patients that were treated at the 1200 mg bid dose, there were no grade 4 or 5 toxicities. Grade 2 and 3 toxicities are listed in Table 2: there was one grade 3 creatinine DLT and grade 2 toxicities included hyperglycemia, fatigue, alopecia, hyperkalemia, mouth sores, shortness of breath, dizziness, nausea, vomiting, ataxia, abdominal pain, headache, and dehydration. For this reason, at the higher doses, tipifarnib was administered along with daily IV hydration in most patients. Assessing potential hematologic toxicities is challenging in AML studies due to the underlying disease, however, among the 3 patients who achieved CR, one patient developed pancytopenia resulting in an episode of febrile neutropenia upon subsequent cycles of drug.

Clinical Activity

The number of patients, DLTs and responses for each individual tipifarnib dose are detailed in Table 3. One patient at the 1000 mg oral bid dose, who had relapsed after autologous stem cell transplant, achieved complete remission (CR) after one cycle, and was taken to allogeneic stem cell transplant, and remains in remission for over five years. There were two CRs achieved at the 1200 mg bid dose: One patient with relapsed disease after standard 7-day cytarabine/ 3-day daunorubicin induction and one cycle of consolidation, entered CR and remained on study for 17 months until relapse; a second patient at the 1200 mg dose level, who had relapsed after first remission, and was resistant to second induction, achieved a CR that lasted one month. Also at the 1200 mg dose level, a third patient patient dropped from 50% to 7% marrow blasts after 3 cycles. At the 800 mg bid dose a patient’s marrow blasts decreased from 36% to 10% over 3 cycles, and at the 1400 mg bid dose bone marrow blasts were decreased by 50% or more in two patients.

Pharmacokinetics

First-dose tipifarnib pharmacokinetic data are available for 10 subjects (Table 4) and 5th dose data for a total of 9 subjects (Table 5). Three subjects received doses of 1400 mg and 7 received 1200 mg bid. The median C_{max} after the 1st dose on Day 1 was 3920 μg/L and 906 μg/L in subjects receiving 1400 mg and 1200 mg, respectively. The median C_{max} after the dose on Day 5 was 2630 μg/L in subjects receiving 1400 mg and 1210 μg/L at the 1200 mg dose level. The median C_{min} after the 1st dose was 237 μg/L and 166 μg/L in subjects receiving 1400 mg and 1200 mg, while the median C_{min} after Day 5 was 476 μg/L and 166 μg/L, respectively. The median AUC_{12h} after the 1st dose was 13,835 hr·μg/L and 4744 hr·μg/L in subjects receiving 1400 mg and 1200 mg, while the median AUC_{12h} after the dose on Day 5 was 17,148 hr·μg/L and 7366 hr·μg/L. The median AUC_{12h} for two patients with decreased blasts was 16295 hr·μg/L and 13221 hr·μg/L on days 1 and 5 respectively, while for the remaining patients, the median AUC_{12h} was 7576 hr·μg/L and 4325 hr·μg/L on days 1 and 5 respectively. Similarly, median Cmax for these two patients was 2442.5·μg/L and 2550 μg/L on days 1 and 5, while median Cmax for the remaining patients was 1290 μg/L and 881 μg/L on days 1 and 5 respectively. These differences were not statistically significant. The median accumulation index in subjects receiving doses of 1400 mg and 1200 mg daily were 1.17 and 1.2, respectively.

Discussion

Tipifarnib is a methylquinolone analogue that competes with the CAAX motif for farnesylation, leading to competitive inhibition of the enzyme farnesyltransferase, which is critical to the function of multiple proteins involved in essential pathways for cell survival. While initially developed as an agent targeting ras, it appears that tipifarnib may act on multiple pathways, and it is possible that its effects on other farnesylated proteins might be enhanced if higher doses of the drug could be delivered in a safe manner. For this reason we studied escalating doses of tipifarnib in a week-on week-off schedule, which maintains the molecular activity of the drug while potentially decreasing toxicity.

In this phase 1 study, consisting almost entirely of patients with relapsed disease, at the 1000 mg and 1200 mg BID dosing levels, we saw 3 CRs, two of which were of long duration, one lasting 17 months and one that enabled the patient to undergo allogeneic stem cell transplant; this patient remains disease free for over 5 years. These three patients all had relapsed disease and cytogenetic abnormalities (trisomy 21, −7, del20). No formal responses were seen among patients treated in the lower dose levels at this schedule.

Tipifarnib pharmacokinetics have been extensively studied at lower doses (13–15), however, relatively few data have been reported for doses above 1000 mg. Karp *et al.* (2) presented data for three subjects receiving 1200 mg and Zujewski *et al.* (4) reported data for 3 subjects given doses of 1300 mg. The results presented here are in general agreement with the earlier studies, and taken together, the data suggest that the pharmacokinetic behavior of tipifarnib is linear up to doses as high as 1400 mg bid. We have also confirmed that relatively modest tipifarnib accumulation occurs between days 1 and 5, even at these higher doses. While the pharmacokinetic sampling did not include the two patients with complete responses at 1200 mg, there was a 2–3 fold higher median AUC and Cmax (on both day 1 and day 5) observed

in the two patients with decreased blasts assayed when compared to the median of the non-responders. The current data also indicate a significant degree of both inter- and intra-patient variability in tipifarnib pharmacokinetics. The potential sources of such variability, as well as its clinical impact, need to be further elucidated.

Although the expansion group is too small (7 patients) to cause concern, it is interesting that no complete responses were seen in this group. However, these were the last patients accrued to the study, raising the theoretical possibility that resistance to tipifarnib could be correlated with prior exposure to hypomethylating agents, which had recently entered standard clinical use. This hypothesis should be examined in a larger study in light of known resistance mechanisms to 5-aza-2'-deoxycytidine (16) and tipifarnib (17).

Tipifarnib is an agent with clear activity in leukemia; however, it is increasingly clear that this activity is limited to disease with certain characteristics, best typified thus far by the correlation with the RASGRP1/APTX ratio as determined by gene signature analysis. Our study suggests that clinical studies designed to study the role of tipifarnib in these populations should consider higher doses on a week-on, week-off schedule.

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Table 1

Patient Characteristics

Patient Characteristics	Number (percent)
Total patients	44(100)
Age in years (median)	61
Age range	33–79
Age < 65 years	24 (55)
Sex	
Male	24 (55)
Female	20 (45)
Race/ethnicity	
Caucasian	34 (77)
Hispanic	6(14)
Asian	4(9)
Median time from diagnosis, months	9.6
Karnofsky performance status (KPS)	
100	11 (25)
90	17(39)
80	11 (25)
70	4(9)
60	1 (2)
Relapsed / refractory disease	41(93)
Prior hematopoietic cell transplant	7(16)
Autologous	5(11)
Allogeneic	2(5)

Table 2

Toxicity grades 2 and above attributable to treatment at 1200 mg bid dose (excluding hematologictoxicities and infection)

	Course 1		Subsequent	
Toxicity	**Grade 2**	**Grade 3**	**Grade 2**	**Grade 3**
ALT, SGPT	2			1
Anorexia	2		1	
AST, SGOT			1	
Ataxia				1
Bilirubin	2		1	
Constipation			1	
Creatinine	2	1	3	
Dehydration	1			
Fatigue	3			2
Febrile neutropenia				1
Hyperglycemia			2	
Hypoalbuminemia	2		2	
Nausea	1	1	2	
Rash / desquamination	1			
Restless leg syndrome			1	
Syncope (fainting)				1
Vomiting	2		2	
Weight loss			1	

Table 3

Outcomes for each tipifarnib dose

Dose (mg bid)	# patients treated	# patients inevaluable	# of cycles median (range)	# DLTs	DLT descriptions	Responses
400	7	1	1 (1–3)	1	hepatic	
600	3	0	3(1–3)	0		
800	5	2	1 (1–3)	0		1 CMML patient cleared leukemic blasts
1000	3	0	2 (2–3)	0		1 CR went to transplant
1200	13	1	2(1–15)	1	renal	2 CRs, 1 marrow response (from 50%-7% blasts)
1400	6	0	3(1–5)	2	renal	2 patients with decreased peripheral blasts
1600	7	2	1 (1–2)	2*	hepatic, renal*	

DLT=dose limiting toxicity, CR=complete remission

*Rapidly progressing grade 2 creatinine was considered dose limiting and dose reduction was initiated.

In all cases, elevation of creatinine reversed during the week off drug.

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Table 4

Day 1 tipifarnib pharmacokinetics

Subject	Dose (mg)	C_{max} (μg/L)	T_{max} (hr)	C_{min} (μg/L)	AUC_{12h} (hr·μg/L)
1	1400	4240	3.1	ND	ND
2	1400	3920	2.0	329	18715
3	1400	1690	3.2	145	8954
	Median =	3920	3.1	237	13835
	Low=	1690	2.0	145	8954
	High=	4240	3.2	329	18715
4	1200	804	2.0	132	3905
5	1200	1180	2.0	339	7727
6	1200	479	2.1	166	3242
7	1200	2300	2.1	ND	ND
8	1200	906	3.0	82	4744
9	1200	3160	3.0	402	15653
10	1200	404	3.0	ND	ND
	Median =	906	2.1	166	4744
	Low=	404	2.0	82	3242
	High=	3160	3.0	402	15653

ND = Not done

Table 5

Day 5 tipifarnib pharmacokinetics

Subject	Dose (mg)	C_{max} (μg/L)	T_{max} (hr)	C_{min} (μg/L)	AUC_{12h} (hr·μg/L)	Accumulation Index
1	1400	ND	ND	ND	ND	ND
2	1400	3890	3.0	781	25589	1.37
3	1400	1370	5.0	170	8707	0.97
	Median =	2630	4.0	476	17148	1.17
	Low=	1370	3.0	170	8707	0.97
	High=	3890	5.0	781	25589	1.37
4	1200	762	3.0	97	4815	1.23
5	1200	995	1.0	204	7001	0.91
6	1200	1880	1.0	234	7787	2.40
7	1200	2500	5.0	283	14233	ND
8	1200	1210	5.0	166	7366	1.55
9	1200	2490	3.1	113	9221	ND
10	1200	1020	2.8	101	4625	ND
	Median =	1210	3.0	166	7366	1.23
	Low=	762	1.0	97	4625	0.59
	High=	2500	5.0	283	14233	1.55

ND = Not done