

# A Phase 1-2 Study of a Farnesyltransferase Inhibitor, Tipifarnib, Combined With Idarubicin and Cytarabine for Patients With Newly Diagnosed Acute Myeloid Leukemia and High-Risk Myelodysplastic Syndrome

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**BACKGROUND:** The authors conducted a phase 1/2 study of tipifarnib in combination with idarubicin and cytarabine (IA) in 95 patients with previously untreated acute myeloid leukemia (AML) or high-risk myelodysplastic syndrome. **METHODS:** Induction consisted of idarubicin 12 mg/m<sup>2</sup> a day on days 1-3, cytarabine 1.5 g/m<sup>2</sup> intravenously continuously daily on days 1-4 (days 1-3 if age  $\geq$ 60 years), and tipifarnib, with the first cohort (n = 6) receiving 200 mg orally twice a day and all others receiving 300 mg twice a day for 21 days every 28 days. Consolidation consisted of 5 courses of idarubicin 8 mg/m<sup>2</sup> a day on days 1-2, cytarabine 0.75 g/m<sup>2</sup> a day on days 1-3, and tipifarnib 300 mg twice a day for 14 days every 4-6 weeks. Maintenance with tipifarnib 300 mg twice a day for 21 days every 4-6 weeks was continued for 6 months. **RESULTS:** With a median follow-up of 33 months, 61 patients achieved complete remission (CR) (64%), and 9 achieved complete remission with incomplete platelet recovery (CRp) (9%). The median duration of CR was not reached. Median overall survival was 17 months. The most common grade 3 adverse events were gastrointestinal toxicities, liver dysfunction, and skin rash. Compared with historical IA, IA and tipifarnib showed a better CR duration ( $P = .04$ ) and a trend toward a higher CR rate in patients with chromosome 5/7 abnormalities. **CONCLUSIONS:** The combination of IA and tipifarnib is safe and active. Further studies exploring different dosages and schedules are warranted, particularly in patients with poor-risk AML. *Cancer* 2011;117:1236-44. © 2010 American Cancer Society.

**KEYWORDS:** acute myeloid leukemia, tipifarnib, combination, myelodysplastic syndrome, farnesyl transferase inhibitor.

The backbone of acute myeloid leukemia (AML) therapy remains centered on cytarabine in combination with an anthracycline such as idarubicin or daunorubicin. Approximately 50% to 70% of patients achieve complete remission (CR), but most will relapse and succumb to their disease or associated complications.<sup>1-3</sup> Patients with high-risk myelodysplastic syndrome (MDS; defined by marrow blasts  $>10\%$ ) are also frequently treated with AML regimens, hypomethylating agents, and/or allogeneic stem cell transplantation. However, they have a poor outcome, with a median survival of 12 months or less.<sup>4-9</sup> Therefore, new therapies and more effective treatment regimens are needed.

Farnesyltransferase inhibitors are a novel class of anticancer agents that competitively inhibit farnesyltransferase (FTase), an enzyme that catalyzes the transfer of a farnesyl moiety to the C-terminal cysteine residue of substrate proteins.<sup>10</sup> A host of intracellular proteins, substrates for prenylation via FTase, play a role in the growth and proliferation of AML cells.<sup>11</sup> Interruption of prenylation may prevent substrates from being functional, which, in turn, may result in the inhibition of cellular events that depend on the function of those substrates. Tipifarnib is an orally available, nonpeptidomimetic farnesyltransferase inhibitor (FTI) with significant in vitro antitumor activity across a wide range of tumors.<sup>12</sup> Tipifarnib has shown clinical activity in myeloid malignancies including in those in elderly patients with AML, high-risk

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MDS, and myeloproliferative disorders.<sup>13-18</sup> In a phase 1 study in patients with refractory leukemias, tipifarnib induced a response rate of 29%, including 2 CRs.<sup>15</sup> The treatment was generally well tolerated, with the major toxicities consisting of mild to moderate myelosuppression, nausea, vomiting, and diarrhea at the maximum tolerated dose (MTD) of 600 mg twice daily. In a phase 2 study using 600 mg twice a day for 21 days every 4 weeks in previously untreated elderly patients and those with refractory or relapsed AML, a CR rate of 14% was reported.<sup>17</sup> In patients with MDS treated at 600 mg twice a day for 28 days every 6 weeks, a response rate of 30% was reported.<sup>16</sup>

The favorable toxicity profile, antileukemic activity, and novel mechanism of action of tipifarnib make it attractive for use in combination therapy. Several studies had suggested a synergy between tipifarnib and chemotherapeutic agents, and FTIs have been suggested to inhibit multidrug resistance, a common mechanism of resistance to chemotherapy in AML, particularly among the elderly.<sup>19,20</sup> In vitro studies showed that the antiproliferative effects in human AML cells are additive when tipifarnib is combined with cladribine or fludarabine<sup>21</sup> and synergistic when tipifarnib is combined with bortezomib<sup>22</sup> or daunorubicin,<sup>20</sup> possibly reflecting, in the latter case, competitive inhibition of P-glycoprotein.

The goal of the current study was to investigate the combination of tipifarnib with an established induction therapy regimen of idarubicin and cytarabine in patients with AML and high-risk MDS.

## MATERIALS AND METHODS

### Study Group

Previously untreated adults with AML (defined by  $\geq 20\%$  blasts) or high-risk MDS ( $> 10\%$  blasts) ages 15 to 70 years were eligible after informed consent was obtained according to institutional guidelines. Previous therapy with hydroxyurea (but no other chemotherapy) and hematopoietic growth factors was allowed. Additional eligibility criteria were: 1) Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1; 2) adequate liver function (serum bilirubin  $\leq 2$  mg/dL, alanine aminotransferase [ALT] or aspartate aminotransferase up to  $2.5 \times$  the upper limit of normal) and renal function (serum creatinine  $\leq 2$  mg/dL); 3) ability to take oral medication; 4) absence of the chromosomal translocation t(15;17); 5) absence of any active and uncontrolled infection or any other severe concurrent disease; and 6) no known allergy to imidazole drugs. Nursing and pregnant women were excluded. Ap-

**Table 1.** Dose Modifications During Induction Therapy

Dose Level	Idarubicin (mg/m <sup>2</sup> /d $\times$ 3)	Cytarabine (g/m <sup>2</sup> /24 h $\times$ 3-4) days	Tipifarnib (mg PO BID $\times$ 21 d every course)
0	12	1.5	300
-1	8	1.0	200
-2	6	0.75	100

proval for the study was granted by the institutional review board of The University of Texas M. D. Anderson Cancer Center. The study was conducted in accordance with the basic principles of the Declaration of Helsinki.

### Treatment Schedule

The treatment plan consisted of induction therapy with cytarabine 1.5 g/m<sup>2</sup> over 24 hours daily on days 1-4 (age  $< 60$  years) or days 1-3 (age  $\geq 60$  years) and idarubicin 12 mg/m<sup>2</sup> intravenously over 1 hour daily on days 1-3. Patients achieving a response received consolidation with 5 additional courses every 4-6 weeks with cytarabine 0.75 g/m<sup>2</sup> over 24 hours daily for 3 days and idarubicin 8 mg/m<sup>2</sup> intravenously over 1 hour daily for 2 days. Tipifarnib was given twice a day for 21 days during induction therapy, for 14 days with each course of consolidation, and as a single agent for maintenance therapy for 3 weeks every 4-6 weeks for 6 courses.

Tipifarnib was given at a dose of 200 mg orally twice a day for the first 6 patients to determine tolerability and at the target dose of 300 mg orally twice a day during induction, consolidation, and maintenance to all other patients after no unexpected toxicity was identified in patients treated at the lower dose. Toxicity was graded according to the NCI Common Terminology Criteria version 3.0. During induction therapy, patients who experienced grades 3-4 extramedullary toxicities, prolonged myelosuppression, or life-threatening myelosuppression-related complications and who were not in CR after 1 course received a second induction course at -2 dose level. Patients who experienced grade 2 extramedullary toxicities received the second course at -1 dose level (Table 1). Patients who developed toxicity requiring dose reduction at the lowest dose level of tipifarnib were taken off the study. Patients who showed no significant antitumor effect after 2 courses were taken off the study. During consolidation, the dose of chemotherapy treatment in subsequent courses was reduced by 25% for grades 3-4 extramedullary toxicities, or for severe life-threatening

infections. The dose of tipifarnib was similarly reduced to the next lower dose, that is, 200 or 100 mg twice a day.

The pretreatment evaluation included history, physical examination, complete blood count (CBC) with differential and platelet count, a complete chemistry survey, and marrow aspiration with cytogenetic analysis. Follow-up studies included CBC, differential, and platelet count as well as chemistry profile every 4-7 days during remission induction and every 1-4 weeks during maintenance therapy. Marrow aspiration and cytogenetics (if abnormal at start) were performed on days 21-28 and then an aspiration every 1-2 weeks as required until CR, then every 3-6 months in year 1. Supportive measures for optimal medical care were provided throughout the study and included admission to a laminar air flow room for the duration of the induction for patients  $\geq 50$  years old, use of prophylactic antibiotics, and irradiated blood-product support as indicated.

### Response Criteria

A CR required bone marrow blasts  $\leq 5\%$  and recovery of normal hematopoiesis with an absolute neutrophil count (ANC) of  $1 \times 10^9/\text{L}$  or more and platelet count of  $100 \times 10^9/\text{L}$  or more in addition to disappearance of all clinical or radiologic evidence of disease. CRp had similar criteria to CR but with platelet counts from 20 to  $<100 \times 10^9/\text{L}$ . Partial response (PR) required blood recovery as for CR but with both a decrease in marrow blasts of  $\geq 50\%$  and  $\leq 25\%$  abnormal cells in the marrow.

### Statistical Analysis

The trial objectives were to assess the safety and tolerability of tipifarnib when used in combination with idarubicin and cytarabine as initial therapy for patients with AML. To further assess the possible impact of adding tipifarnib, results were compared with a historical cohort of patients treated with the same chemotherapy but without tipifarnib. The impact of clinical features on outcome was an exploratory endpoint.

Because this combination had not been used before, an initial cohort of 6 patients was first treated at a reduced dose of tipifarnib. Once the lower-dose tipifarnib combination was determined to be safe, patients were treated with the target dose (ie, 300 mg twice a day) to a maximum of 90 patients. The target dose would start accrual if grades 3-4 toxicity attributable to tipifarnib was observed in fewer than 2 of the 6 patients treated at the 200-mg twice-daily dose. Patients who were eligible for the trial and received any dose of idarubicin, cytarabine, or tipifarnib were included in estimating CR rates and were counted as treat-

ment failures if response could not be assessed for any reason. Duration of CR and overall survival were estimated according to the Kaplan-Meier method. CR duration was dated from the start of CR to first evidence of recurrence. The efficacy and toxicity profile of this combination were compared with the historical M. D. Anderson experience with 108 consecutive patients having the same inclusion criteria and treated with the same chemotherapy without tipifarnib between 2001 and 2005.

For the phase 2 portion of the study, the design was adapted to account for patient characteristics. The trial would be terminated after the first 45 patients were evaluated if 20 or fewer CRs were observed. With the trial continuing to maximum accrual of 90 patients, the combination regimen would be recommended for further study in this group of patients if at least 58 CRs were observed. The probability that the combination would be recommended under the assumption of a CR rate of 74% was .91. Outcome by other disease characteristics was assessed in a descriptive manner.

## RESULTS

### Study Group

A total of 95 patients were enrolled in the study: 6 at the lower dose and 89 at the target tipifarnib dose of 300 mg twice a day. The patient characteristics are summarized in Table 2. The median age was 50 years (range, 17-61 years). Sixty-three patients (66%) had an ECOG performance status of 1. There were 82 patients with AML as defined by the World Health Organization classification ( $\geq 20\%$  blasts as the cutoff between AML and high-risk MDS). Forty patients (42%) had antecedent hematologic disorders prior to their diagnosis, for a median of 2 months (range, 1-108 months). More than half the patients had abnormal karyotypes, which included abnormalities of chromosomes 5 and/or 7 in 19 patients (20%), translocation t(8:21) in 2 (2%), inversion 16 in 3 (3%), and other abnormalities in 29 (31%). Of 83 patients whose marrow samples were tested for *FLT3* abnormalities, 13 (16%) showed internal tandem duplications (ITDs), and 6 (7%) showed mutations in aspartic acid residue 835 (D835) of the tyrosine kinase loop (2 patients had both mutations).

### Response and Outcome

Sixty-one patients (64%) achieved CR and 9 (9%) CRp, for an overall response rate of 74%. Twenty-one patients (22%) had resistant disease, and 4 (4%) died during

**Table 2.** Patient Characteristics

		Median (range)/N (%)		
Parameter		IA+Tipifarnib, N=95	IA (Historical Control), N=108	P
Age (y)		50 (17-61)	52 (17-61)	.517
PS (1)		63 (66)	59 (55)	.089
WBCs ( $\times 10^9/L$ )		5.3 (0.5-161.5)	10.0 (0.5-390.0)	.047
Platelets ( $\times 10^9/L$ )		62 (9-676)	58 (5-635)	.159
AHD (mo)		2 (1-108)	0 (0-144)	.807
		40 (42)	38 (35)	.312
Disease type	AML	82 (86)	100 (93)	.144
	MDS	13 (14)	8 (7)	
CG	Diploid	41 (43)	56 (52)	.617
	t(8;21)/inversion 16	5 (5)	3 (3)	
	Chromosome 5 or 7 abnormalities	19 (20)	16 (15)	
	Other	29 (31)	31 (29)	
	Not done	1 (1)	2 (2)	
FLT3 (+) <sup>a</sup>	ITD	13/83 (16)	18/57 (32)	.080
	Point mutation	6/83 (7)	4/57 (7)	

IA, idarubicin and cytarabine; ECOG PS, performance status; WBCs, white blood cells; AHD, antecedent of hematologic disorder; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; CG, cytogenetic; inv, inversion; ITD, internal tandem duplication.

<sup>a</sup>Two patients had both mutations on IA+tipifarnib; 1 patient had both mutations on IA.

**Table 3.** Responses to Idarubicin, Cytarabine, and Tipifarnib by Disease Characteristics

Parameter	No.	CR (%)
Overall	95	61 (64)
<b>Karyotype</b>		
Diploid	41	30 (73)
Chromosome 5 or 7 abnormalities	19	11 (58)
t(8;21)/inversion 16	5	4 (80)
Other abnormalities	29	16 (55)
Not done	1	0 (0)
<b>FLT3 status</b>		
Mutated	17	13 (76)
Wild type	66	44 (67)
Not done	12	4 (33)
<b>Group</b>		
<50 y	43	31 (72)
≥50 y, diploid	18	12 (67)
≥50 y, other	34	18 (53)

CR indicates complete response.

induction, on days 8, 11, 27, and 55, for a failure rate of 26% (Table 3). Of 41 patients with diploid cytogenetics, 30 (73%) had CR and 4 (10%) CRp (OR, 83%). The CR rate was 58% (11 of 19) in patients with abnormalities of chromosomes 5 and/or 7 and 55% (16 of 29) in those harboring other cytogenetic abnormalities. The CR rates were 72% in 43 patients younger than 50 years, 67% in 18 patients older than 50 years with diploid cytogenetic

analysis, and 53% in 34 patients older than 50 years with unfavorable cytogenetic analysis. Seventeen patients had abnormalities of *FLT3* in the form of ITDs and/or D835. CR rates were 67% (44 of 66) in *FLT3* wild-type patients and 76% (13 of 17) in those with *FLT3* mutations.

Three patients (1 diploid and 2 abnormal cytogenetics) who failed to achieve CR following the first induction course received a second induction with identical doses and schedules of tipifarnib and IA; none of them achieved CR. Median time to CR was 30 days (range, 21-71 days) for all patients, 29 days (range, 21 to 60 days) in the diploid group, and 34 days (range, 23-71 days) in the abnormal cytogenetic group. Median time to CRp was 31 days (range, 18-67 days).

Four patients (4%) died during the first induction course. One patient (age 43 years) had an acute myocardial infarction, followed by congestive heart failure, and died on day 8 of the induction course. A 28-year-old patient had sepsis, with disseminated intravascular coagulopathy, and died on day 11. One 52-year-old patient developed a diffuse alveolar hemorrhage and probable fungal pneumonia and died on day 27. One patient (age 44 years) had concomitant bacterial and fungal septicemia that led to multiple organ failure; he died on day 55 before recovering his counts.

Overall, 70 patients received a total of 152 courses of consolidation therapy. Seventeen patients received only

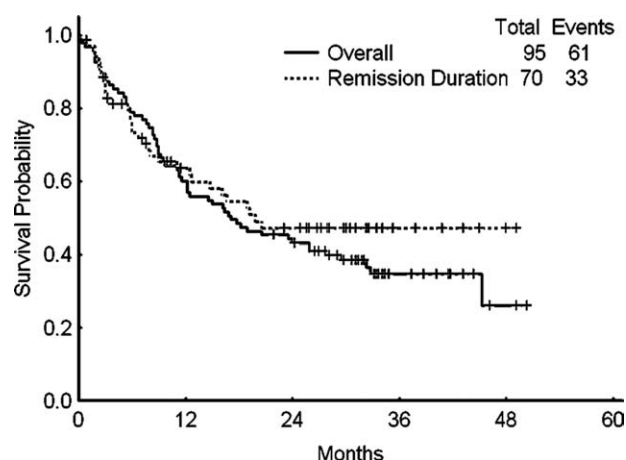


Figure 1. Survival and remission duration are shown.

1 cycle of consolidation, 9 received 2, and 26 received 3 or more, with 19 completing all 5 planned cycles. The main reasons for not completing consolidation chemotherapy as planned were allogeneic stem cell transplantation ( $n = 18$ ), treatment toxicities ( $n = 14$ ), and disease relapse ( $n = 13$ ). Seventeen patients received a total of 82 courses of maintenance therapy with tipifarnib at a median dose of 100 mg twice a day (range, 100-200 mg twice a day), for a median of 5 months (range, 1-8 months). Of the 17 patients, 8 remained in remission for 50+ months (range, 45 to 64+ months), whereas 9 patients relapsed after a median of 18 months (range, 12-34 months), 5 of whom later died after a median of 22 months (range, 14-34 months). Eighteen patients (median age, 52 years; range, 34-60 years) received consolidation therapy with allogeneic stem cell transplantation: 16 in CR and 2 in CRp. Five of them (28%) had chromosome 5 or 7 abnormalities compared with 14 of 77 (18%) who did not receive transplantation ( $P = .16$ ). Of the 18 transplanted patients, 6 (33%; 1 with chromosome 7 abnormality) were alive 22+ months (range, 11 to 33+ months) after transplantation, 5 (28%) relapsed and died, and 7 (39%) died in CR or CRp of transplant-related complications.

With a median follow-up of 33 months (range, 23-50 months), 27 of 61 patients who achieved CR (44%) were still in remission (6 after transplant). The median remission duration for all patients who achieved CR was not reached (range, 1 to >49 months). In contrast, patients who achieved CRp had a median remission duration of only 3 months (range, 1-35 months). Median overall survival for the intent-to-treat population was 17 months (range, 0 to >50 months). Median overall sur-

Table 4. Adverse Events in  $\geq 5\%$  of All Patients During Induction (Regardless of Causality)

Adverse Events During Induction	Any Grade	Grade $\geq 3$
	No.	No.
Diarrhea	68	33
Nausea/vomiting	56	9
Rash/pruritis	51	18
Hepatic (bilirubin/SGPT)	31	13
Mucositis/stomatitis/colitis/gastritis	29	10
Pain	28	5
Fatigue	20	7
Neurologic (anxiety, mood alteration, seizure, vision)	15	3
Cardiac	15	1
Hypokalemia	14	13
Edema	12	1
Respiratory	11	2
Constipation	11	0
Hypoalbuminemia	10	3
Hyperglycemia	10	2
Hypophosphatemia	8	6
Anorexia/weight loss	8	2
Renal	8	1
Hypocalcemia	6	2
Hemorrhage/bleeding	5	3

vival was 32 months (range, 2 to >50 months) for those patients who achieved CR, 12 months (range, 2 to >43 months) for those who achieved CRp, and 8 months (range, 0 to >34 months) for nonresponders (Fig. 1).

### Side Effects

No grades 3-4 tipifarnib-related toxicities were observed among the first 6 patients enrolled in the phase 1 portion of the study and who received tipifarnib 200 mg twice a day; therefore, the dose of tipifarnib was increased to 300 mg twice a day and was given to 89 patients enrolled in part 2 of the study. Table 4 summarizes the toxicities observed with the combination therapy during induction. The most frequently observed side effects were diarrhea, nausea and vomiting, skin rash, mucositis, and hyperbilirubinemia. Tipifarnib was held for a median of 5 days (range, 0-18 days) during induction therapy. Fifty-three patients (56%) had tipifarnib dose reductions during induction, 21 (40%) during consolidation, and 3 (18%) during maintenance. The most common causes for treatment interruption and dose reduction were gastrointestinal toxicities, prolonged myelosuppression, and sepsis. During consolidation, the median time to neutrophil recovery ( $ANC \geq 1 \times 10^9/L$ ) was 26 days (range, 0-64 days) and for platelet recovery ( $\geq 100 \times 10^9/L$ ) was 37 days (range, 0-65 days). Neutropenia and thrombocytopenia



**Table 5.** Comparison with Age and Treatment-Era Matched Patients Who Received Idarubicin and Cytarabine

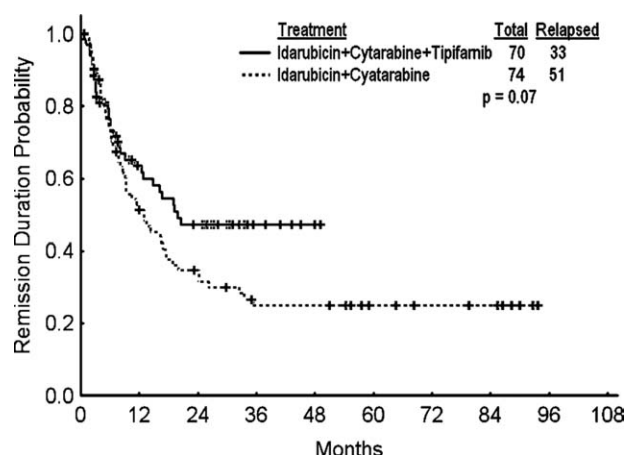
	Idarubicin and Cytarabine (CI)	Idarubicin, Cytarabine, and Tipifarnib (CI)	P
<b>Overall, no.</b>	108	95	
CR rate, %	60 (50-69)	64 (54-74)	.59
OR rate, %	70 (59-77)	74 (54-74)	
Median CRD, mo	13 (12.9-13.1)	NR	.04
Median, OS, mo	13 (12.7-13.1)	17 (16.9-17.2)	.27
<b>Diploid, no.</b>	56	41	
CR rate, %	75 (62-86)	73 (57-86)	.23
OR rate, %	77 (64-87)	83 (68-93)	
<b>Chromosome 5 or 7 abnormalities, no.</b>	16	19	
CR rate, %	19 (4-46)	58 (34-80)	.054
OR rate, %	32 (11-59)	69 (43-87)	

CI indicates confidence interval; T, tipifarnib; CR, complete response; OR, objective response; CRD, complete response duration; OS, overall survival; NR, not reached.

grades 3-4 during maintenance therapy were uncommon. Median time to next course was 43 days (range, 15-161 days) during consolidation and 32 days (range, 24-154 days) during maintenance. Tipifarnib was given at a dose of 200 mg twice a day in 96 of the 152 cycles of consolidation (63%) and in 44 of the 83 cycles of maintenance (53%) and at 100 mg twice a day in 31 cycles of consolidation (20%) and in 23 cycles of maintenance (28%).

### Comparison With Historical Patients Receiving Idarubicin and Cytarabine

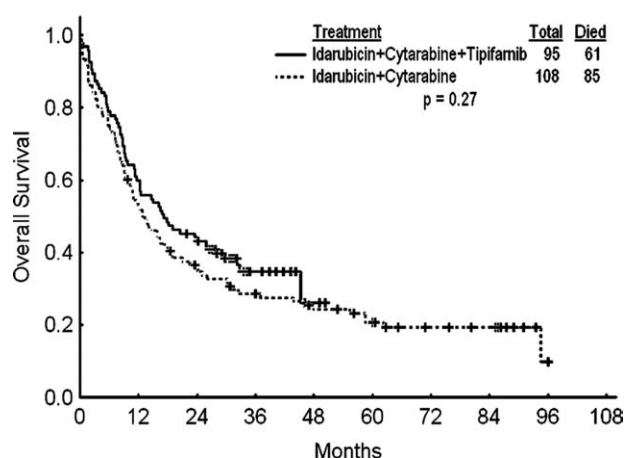
We compared the efficacy and safety of tipifarnib-based combination with historical experience at M. D. Anderson using the same chemotherapy without tipifarnib in matched patients (by age and year of treatment) receiving idarubicin and cytarabine therapy (Table 5). The objective response rates were similar. There was a trend for higher CR rates in favor of patients with chromosome 5 and 7 abnormalities treated with the tipifarnib-based combination (58% vs 19%;  $P = .054$ ), but there was no effect on survival ( $P = .12$ ). The median number of consolidation courses for patients who achieved CR treated with chemotherapy was 3 (range, 1-5), compared with 4 (range, 0-4) for those in the historical control group. There was a better median complete remission duration (CRD) with the tipifarnib-based combinations: the median CRD was not reached for patients treated with tipifarnib-based combinations and was 13 months with chemotherapy alone ( $P = .04$ ); the 18-month CRD rates were 54% and 38%, respectively (Fig. 2). Median overall survival rates were 17 versus 13 months; the 18-month

**Figure 2.** Remission duration with idarubicin and cytarabine versus with idarubicin, cytarabine, and tipifarnib (including patients in CR and CRp) is shown.

survival rates were 48% and 41% ( $P = .27$ ; Fig. 3). Patients receiving tipifarnib-based combinations had a higher rate of grades 3-4 diarrhea (35% versus 8%;  $P < .001$ ). The 6- and 12-week mortality rates were 3% and 12%, respectively, with the tipifarnib-based therapy versus 8% and 16%, respectively, with chemotherapy alone ( $P = .27$ ).

## DISCUSSION

This study evaluated the efficacy and safety of a combination therapy of tipifarnib, idarubicin, and cytarabine in adults with AML. Prior investigations using single-agent tipifarnib at a dose of 600 mg orally twice a day for 21



**Figure 3.** Overall survival idarubicin and cytarabine versus with idarubicin, cytarabine, and tipifarnib is shown.

days every 28-day cycle, reported CR rates of 4% in patients with refractory disease and 14% in elderly patients with previously untreated AML.<sup>17-23</sup> In this study, using tipifarnib 300 mg orally twice a day in combination with idarubicin and cytarabine, a CR rate of 64% was achieved with an acceptable safety profile. Median survival was 17 months, and median CR duration was 19 months.

Overall, this study did not demonstrate any significantly increased antileukemia activity with the addition of tipifarnib. Except for a possible trend toward more durable responses with the tipifarnib-based combination compared with historical controls, the CR and survival rates were not different from what would be expected with chemotherapy alone. In our study, the dose of tipifarnib was 300 mg twice a day, lower than the MTD identified in the phase 1 trial (600 mg twice a day given for 21 days every 28 days), and in more than 50% of the consolidation courses, tipifarnib was reduced to 100-200 mg twice a day. A recent report found no apparent increase in response rate with higher tipifarnib doses when used as a single agent; therefore, the benefit of a higher dose intensity is unclear.<sup>24</sup> Despite the possible trend for more durable responses, the role of tipifarnib and the contribution of the extended therapy during consolidation and maintenance can only be assessed in a randomized trial.

Other studies have failed also to demonstrate a considerable benefit of tipifarnib used alone or in combination with chemotherapy. Brandwein et al failed to show a significant benefit by adding tipifarnib to chemotherapy.<sup>25</sup> In their study, the combination of tipifarnib, given at a dose of 600 mg twice a day for 10 days per cycle, and

conventional “3 + 7” induced an objective response rate of 54% in previously untreated patients with AML ages 60 years and older; this rate was not significantly different from what was obtained with chemotherapy alone. A phase 3 randomized trial in patients with AML aged 70 years and older randomized to tipifarnib versus best supportive care did not show a survival advantage for tipifarnib. The CR rate in that study was only 8%.<sup>26</sup>

Although the response rates to tipifarnib as a single agent may be independent of the cytogenetic risk group,<sup>17</sup> the CR rate in the present study for patients with adverse risk cytogenetics (58%) was higher than the response rate of 19% in patients treated with identical chemotherapy in the historical cohort. This is in line with a previous report from Brandwein et al, who reported a response rate of 57% in patients receiving tipifarnib-based combination versus 30% in patients treated with standard induction regimen.<sup>25</sup> Karp et al also reported that tipifarnib maintenance may benefit patients with secondary AML and adverse cytogenetics; the CRD was longer in patients who received tipifarnib maintenance therapy compared with that in the historical control (HR, 0.11;  $P = .02$ ).<sup>27</sup> Based on these observations, patients with adverse cytogenetics might be a subset in whom further exploration of tipifarnib-based chemotherapy combinations may be warranted. Furthermore, Raponi and colleagues have identified and validated a 2-gene expression ratio, *RASGRP1/APTX*, that has predictive utility in both newly diagnosed and relapsed or refractory AML treated with tipifarnib.<sup>28</sup> The stratification with this classifier significantly predicts for improved overall survival that is independent of other prognostic factors including a previously described genomic signature. Similarly, in 11 patients with relapsed/refractory mantle cell lymphoma treated with tipifarnib, the *RASGRP1/APTX* gene expression ratio was higher in the responder, whereas *AKAP13* expression was higher in the nonresponders.<sup>29</sup> This gene analysis was not available for the present study, but it is possible that patients could be selected this way in future studies to identify those most likely to benefit.

The combination regimen was well tolerated. The major toxicities were gastrointestinal, including transient liver test abnormalities, nausea and vomiting, diarrhea, and mucositis. Except for diarrhea, the toxicities were not substantially more than those observed with standard chemotherapy alone. Gastrointestinal toxicities were frequently seen with tipifarnib single-agent therapy, although this was observed at higher doses.<sup>15</sup> In a recent phase 1 study combining tipifarnib and standard

induction therapy in elderly patients, more severe gastrointestinal toxicities were reported at a dose of 600 mg twice a day.<sup>25</sup> Although myelosuppression is a common toxicity of tipifarnib, there was no significant prolonged myelosuppression, and the median time to neutrophil and platelet recovery was comparable to that observed with standard chemotherapy alone. There was no increase in the 6- and 12-week mortality rates.

In summary, the results of this study suggest that the combination of idarubicin, cytarabine, and tipifarnib in patients with AML and high-risk MDS can be safely administered. A possible benefit of this combination among patients with high-risk cytogenetic abnormalities deserves additional investigation.

## CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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