A phase I study of idarubicin dose escalation with amifostine and high-dose cytarabine in patients with relapsed acute myelogenous leukemia and myelodysplastic syndromes

GUILLERMO GARCIA-MANERO, STEFAN FADERL, FRANCIS GILES,
DEBORAH THOMAS, JORGE CORTES, SUSAN O'BRIEN,
JAN DAVIS, HAGOP M. KANTARJIAN, ELIHU ESTEY
Department of Leukemia, University of Texas M.D. Anderson
Cancer Center, Houston, TX, USA

Background and Objectives. Early studies have suggested that increasing doses of anthracycline improve outcome in younger patients with acute myelogenous leukemia (AML), but dose escalation has been precluded by the acute and chronic toxicities of these agents. Amifostine is a cytoprotective compound that has been shown to protect against the acute cytotoxicities of anthracyclines in animal models. We report the results of a phase I study of dose escalation of idarubicin with amifostine and high-dose ara-C in patients with relapsed or refractory AML or myelodysplastic syndrome (MDS).

Design and Methods. The continuous reassessment method was used to predict the probability of toxicity.

Results. Five patients were treated at an idarubicin dose of 18 mg/m^2/day × 3, three of whom developed grade 3 diarrhea or mucositis. Subsequently, three additional patients were treated at a dose of 15 mg/m^2 × 3 days, all of whom experienced grade 3 diarrhea or mucositis. One patient achieved complete remission (CR rate 12.5%, 95% CI 0-0.52%).

Interpretation and Conclusions. The addition of amifostine does not allow dose escalation of idarubicin when combined with high-dose ara-C.
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Key words: acute myelogenous leukemia, myelodysplastic syndrome, amifostine, idarubicin, cytarabine.

Correspondence: Guillermo Garcia-Manero, M.D., Department of Leukemia, University of Texas M.D. Anderson Cancer Center, Box 428, 1515 Holcombe Blvd Houston, TX, USA 77030. Phone: international +1.713.7453428. Fax: international +1.713.7944297. E-mail: ggarciam@mdanderson.org

Chemotherapy for patients with AML usually consists of an anthracycline and ara-C.[1] While intensification of the ara-C dose has been studied extensively, intensification of the anthracycline dose has received less attention.[2] A randomized study has suggested a dose-response effect at least for younger patients,[3] but anthracycline-dose intensification has been limited by the acute and chronic toxicities characteristic of these agents. When used as a cytoprotective agent, amifostine (WR-2721; S-2-[3-minopropylamino] ethyl-phosphorothioic acid) protects normal tissues from the effects of alkylating agents and platinum-based drugs[4,5] and diminishes acute anthracycline-related toxicities in animal models.[6] Investigators at Thomas Jefferson University Hospital (TJUH) are determining the maximally tolerated dose (MTD) of idarubicin when given with amifostine and standard dose ara-C (100 mg/m^2/day ×7) to newly diagnosed patients with high-risk AML. As most recently reported,[7] the dose of idarubicin had been escalated to 19 mg/m^2/day ×3 without dose-limiting toxicity (DLT).

In view of this experience, we designed a phase I study to determine whether addition of amifostine would permit dose escalation of idarubicin when combined with higher ara-C doses than used in the TJUH study.

Design and Methods

Study group

Patients with refractory anemia with excess blasts (RAEB), RAEB in transformation (RAEB-T) or AML were eligible if they were younger than 60 years of age, had serum and creatinine each < 3 mg/mL, performance status ≤3 (ECOG scale), and a cardiac ejection fraction of more than 30%, without a history of uncontrolled arrhythmias, or cardiac conduction abnormalities. All patients provided informed consent following institutional guidelines.

Patients were monitored daily during therapy, and at least 3 times weekly thereafter until stabilization of peripheral blood counts. Monitoring included complete blood count (CBC) and serum chemistries, including ionized calcium. Bone marrow aspiration was performed on days 21 and 28, and then as needed to document response.

Therapy

The doses of ara-C and amifostine were fixed, respectively, at 1.5 g/m^2/day days 1-4 continuous infusion (CI), and 910 mg/m^2 prior to each dose of idarubicin. The starting dose (dose level 0) of idarubicin was 18 mg/m^2/day on days 1, 2 and 3, this dose being 1 mg/m^2 below the highest dose reported in the TJUH study. Dose level 1 was 21 mg/m^2/day ×3, and dose level –1 was 15 mg/m^2/day ×3. Amifostine was infused over 5 minutes, 15 minutes before each dose of idarubicin. Amifostine premedications included ondasentron, dexamethasone 20 mg, lorazepam 0.5 mg, diphenhydramine 25 mg, and ranitidine 50 mg, all 30 minutes prior to the amifostine infusion. Antihypertensive medications were stopped 24 hours prior to infusion. Patients received intravenous fluids at a rate of 100-200 cc/hour for 1 to 2 hours prior to the amifostine infusion. The patient's blood pressure was monitored every 2 minutes during the amifostine infusion. Complete response was defined using standard criteria.[8]

Study design and statistical analysis

The study was conducted using the continuous reassessment method (CRM).[9] With the CRM method, the investigator specifies prior probabilities of toxicity at each planned dose level. Previous experience suggested a 10% rate of toxicity, as defined below, in similarly aged patients given idarubicin 12 mg/m^2/day × 3 and ara-C 1.5 g/m^2/day CI × 4 days. With the addition of amifostine, we predicted a 10% probability of toxicity at an idarubicin dose of 15 mg/m^2/day × 3. Similarly, our prior probabilities of toxicity at 18 and 21 mg/m^2 were 0.25 and 0.5. The investigator also determines a target probability of toxicity. We chose 0.25; thus at our MTD there would be a 0.25 probability of toxicity. This is intermediate between the rates of 0.17 (1/6) and 0.33 (2/6) specified by the 3+3 phase I algorithm. Before beginning the trial, level 0 was associated with the target 0.25 probability of toxicity, so the trial began at this dose level. The toxicity experience (yes/no) gained in the first 3 patients at this dose level was then incorporated into the prior probability of toxicity to give a posterior probability of toxicity. This was

Table 1. Operating characteristics of statistical design.

Scenario	Dose level	True probability of toxicity	Probability of declaring a dose as MTD
1	–1	0.1	0.20
	0	0.25	0.73
	1	0.50	0.07
2	–1	0.5	0.96
	0	0.75	0.04
	1	0.9	0
3	–1	0.01	0.01
	0	0.1	0.39
	1	0.25	0.6

Dose level –1= 15 mg/m^2/day × 3; dose level 0= 18 mg/m^2/day × 3; dose level 1= mg/m^2/day × 3. MTD, maximally tolerated dose.

done using the model of O'Quigley.[9] The level closest to 0.25 was then chosen as the level for the next 3 patients. The process was to be repeated until a maximum of 30 patients had been treated or until 6 had been treated at a dose whose posterior probability of toxicity was approximately 0.25. The characteristics of our design given various true probabilities of toxicity are shown in Table 1. In all cases examined, the dose whose true probability of toxicity was closest to 0.25 was most likely to be selected, although in scenario 2 (each dose above the desired 0.25), the design identified the MTD as a dose with a true probability of toxicity of 0.5. Toxicities were graded using the National Cancer Institute criteria. Grade 4 hematologic toxicity was considered present if the time to recovery of neutrophils (> 0.5×10^9/L) or platelets (> 50×10^9/L) exceeded 49 days, provided the marrow had less than 10% blasts. Nausea and vomiting were not considered dose-limiting toxicity.

Results

Study group

Eight patients were treated. Their median age was 44.5 years (range 22 to 54). The median bone marrow blast percentage prior to therapy was 60% (range 23% to 89%). Four patients had primary resistant disease. The median duration of first CR was 4 months (range 0-16). The median number of salvage treatments was 1.5 (range 0-4) (Table 2).

Responses

One patient achieved a CR (CR rate 12.5%, 95% CI 0-0.52%), but had central nervous system recurrence 1 month later and subsequently died. No

Table 2. Patients' characteristics.

Pt.	Dose	Age	% BM blasts	WBC × 10⁹/L	CG	Duration of CR #1	Duration of CR #1 postRx	Duration of CR#2	No. salvage treatments
#1	18	47	89	42.8	Diploid	8	1	0	2
#2	18	54	41	14.8	Diploid	12	6		0
#3	18	32	62	127.7	IM	0			4
#4	18	22	83	4.7	Diploid	16	9	2	2
#5	18	45	60	100.5	-7, hypo	0			2
#6	15	41	81	1.5	Diploid	0			1
#7	15	50	54	1.7	-7, pseudo	0			1
#8	15	44	23	7.2	-7, pseudo	12	3		0

*Pt, patients; idarubicin dose in mg/m²/day × 3; age in years; BM, bone marrow; CG, cytogenetics at initial presentation; CR, complete remission; postRX, after finishing all chemotherapy; *duration also in months; IM: insufficient metaphases.*

patient died within the first 2 weeks of treatment, but 5 died with hypoplastic marrows.

Toxicities

Toxicities for each dose and patient are summarized in Table 3. Three out of 5 patients treated at dose level 0 had grade 3 mucositis or diarrhea. All three patients treated at dose level –1 had grade 3 mucositis or diarrhea. One patient developed atrial fibrillation at dose level –1. Hypotension was not observed.

Table 4 shows the prior and posterior probabilities of toxicity for each patient at each dose level. For example since patient #1 had no toxicity, the posterior probabilities are lower than the prior ones. These posterior probabilities then form the prior ones for the next patient. After entry of the first cohort of 3 patients, the level whose posterior probability of toxicity was closest to 0.25 was level 0. Thus the second cohort of 3 was to be treated at that level. However after entry of the 5th patient, the posterior probability of toxicity at level 0 was 0.53 (Table 4). Therefore we decided to treat a new cohort of 3 patients at dose level –1 instead of treating the sixth patient at dose level 0. Each of 3 patients at dose level –1 had toxicity. Thus the posterior probabilities of toxicity after accounting for data from all 8 patients were 0.52, 0.78, and 0.92 at levels –1, 0, and 1, respectively. Since each was above the 0.25 target none of the 3 levels would be recommended as MTD.

Discussion

Our observations of severe toxicities, mainly mucositis and diarrhea, at doses of idarubicin higher than 12 mg/m²/day × 3, the accepted MTD, contrast with the observations of the previously reported study.[7] There are several possible explanations for this discrepancy. First, our dose of ara-C was higher than the dose used by Flomenberg et al.[7] In this context it is noteworthy that the pharmacokinetics of amifostine do not predict that the drug will be cytoprotective against ara-C toxicities when given as a continuous infusion. However, in our experience these doses of ara-C, when used with idarubicin at 12 mg/m²/day × 3, produce only a 10% incidence of grade 3 or 4 mucositis or diarrhea. Hence it is possible that the toxicities observed here reflect synergy between ara-C at the dose we used and idarubicin given at a dose of 15 mg/m²/day × 3 or greater. Second, the patients differed in the two studies, with our patients having relapsed/refractory disease but also being younger. Third, reporting of toxicity may have varied with time so the incidence of toxicity with ara-C 1.5 g/m²/day × 4 and idarubicin 12 mg/m²/day × 3 was higher than the historical rate of 10% noted above.

It is important to note that our study does not exclude that amifostine may have cytoprotective

Table 3. Toxicities.

Patient	Dose	Mucositis grade	Diarrhea grade	Cardiac	Hypotension	N/V	Others
1	18	0	0	0	0	1	0
2	18	1	1	0	0	1	2 biliary; 2 creatinine
3	18	3	1	0	0	1	1 pruritus
4	18	3	2	0	0	0	1 rash; 2 ataxia
5	18	3	2	0	0	2	0
6	15	2	3	3	0	3	0
7	15	1	3	0	0	2	0
8	15	3	1	0	0	1	0

Idarubicin dose levels in mg/m²/day × 3. Toxicities using NCI criteria; N/V, nausea and vomiting.

Table 4. Probabilities of toxicity.

Pt.	Dose	Toxicity	Dose level –1		Dose level 0		Dose level 1	
			Prior	Posterior	Prior	Posterior	Prior	Posterior
#1	18	No	.1	.04	.25	.15	0.5	.4
#2	18	No	.04	.02	.15	.1	0.4	.34
#3	18	Yes	.02	.09	.1	.34	.34	.68
#4	18	Yes	.09	.16	.34	.45	.68	.77
#5	18	Yes	0.16	.22	.45	.53	.77	.81
#6	15	Yes	.22	.35	.53	.66	.81	.87
#7	15	Yes	0.35	.45	.66	.73	.87	.9
#8	15	Yes	0.45	.52	.73	.78	.9	.92

Dose in mg/m²/day x 3. Dose level –1= 15 mg/m²/day × 3; dose level 0= 18 mg/m²/day × 3; dose level 1= 21 mg/m²/day × 3. Toxicity was considered if it was ≥ grade 3 as defined by the NCI. Prior, prior probability of toxicity; posterior; posterior probability of toxicity.

effects when combined with high dose ara-C given as a pulse, or with other anthracyclines or analogs such as daunorubicin or mitoxantrone. We selected the studied schedule because in our experience this is our most active combination, and is routinely offered in our institution to newly diagnosed patients with AML who do not qualify for clinical trials.

In summary, amifostine does not allow idarubicin dose escalation when combined with the doses of ara-C administered in this study, and should not be studied further in this setting. It will be important to wait for the long-term results in terms of remission duration and chronic sequelae of anthracycline use in ongoing studies at other centers using lower doses of ara-C with amifostine.

Contributions and Acknowledgments

GGM and EE designed the study. All the authors contributed to data analysis and interpretation, and to the preparation of the final manuscript. GGM was the principal investigator of the study.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

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PEER REVIEW OUTCOMES

Manuscript processing

This manuscript was peer-reviewed by two external referees and by Professor Theo De Witte, who acted as an Associate Editor. The final decision to accept this paper for publication was taken jointly by Professor De Witte and the Editors. Manuscript received May 8, 2002; accepted June 19, 2002.

What is already known on this topic

The extramedullary dose-limiting toxicity of the combination of high dose Ara-C and increasing dosages of idarubicin is oral and intestinal mucositis. Amifostine has been described to prevent chemotherapy-induced mucositis.

What this study adds

This study shows that this schedule of amifostine (910 mg/m² prior to each dose of idarubicin) does not prevent grade 3/4 mucositis at the dose level of 15 mg/m²/d idarubicin.

Potential implications for clinical practice

Other schedules of amifostine may be more appropriate considering the long half-life time of idarubicin and its major active metabolite idarubicinol.

Theo De Witte, Associate Editor