Adaptive Randomized Study of Idarubicin and Cytarabine Versus Troxacitabine and Cytarabine Versus Troxacitabine and Idarubicin in Untreated Patients 50 Years or Older With Adverse Karyotype Acute Myeloid Leukemia

By Francis J. Giles, Hagop M. Kantarjian, Jorge E. Cortes, Guillermo Garcia-Manero, Srdan Verstovsek, Stefan Faderl, Deborah A. Thomas, Alessandra Ferrajoli, Susan O'Brien, Jay K. Wathen, Lian-Chun Xiao, Donald A. Berry, and Elihu H. Estey

Purpose: **Troxacitabine has activity in refractory myeloid leukemia, either as a single agent or when combined with cytarabine (ara-C) or with idarubicin. A prospective, randomized study was conducted in patients aged 50 years or older with untreated, adverse karyotype, acute myeloid leukemia (AML) to assess troxacitabine-based regimes as induction therapy.**

Patients and Methods: **Patients were randomized to receive idarubicin and ara-C (IA) versus troxacitabine and ara-C (TA) versus troxacitabine and idarubicin (TI). A Bayesian design was used to adaptively randomly assign patients to treatment. Thus, although there was initially an equal chance for randomization to IA, TA, or TI, treatment arms with a higher success rate progressively received a greater proportion of patients.**

Results: **Thirty-four patients were treated. Randomization to TI stopped after five patients and randomization to TA stopped after 11 patients. Defining success as complete remission (CR) that occurred within 49 days of starting treatment, success rates were 55% (10 of 18 patients) with IA, 27% (three of 11 patients) with TA, and 0% (zero of five patients) with TI. Because three CRs occurred after day 49, final CR rates were 55% (10 of 18 patients) with IA, 45% (five of 11 patients) with TA, and 20% (one of five patients) with TI. The probability that TA was inferior to IA was 70%, with a 5% probability that TA would have a 20% higher CR rate than IA. Survival was equivalent with all three regimens.**

Conclusion: **Neither troxacitabine combination was superior to IA in elderly patients with previously untreated adverse karyotype AML.**

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ALL NUCLEOSIDE analogues currently approved as anticancer agents are in the D configuration.[1] The discovery of lamivudine as a potent inhibitor of human immunodeficiency virus 1 (HIV-1) reverse transcriptase led to both the acceptance that unnaturally configured nucleoside analogs could be metabolized by humans and to the development of L-enantiomers as anticancer agents.[2,3] Modification of the structure of lamivudine resulted in the formation of troxacitabine, which has antileukemia activity.[4-8] In a phase I study of troxacitabine in patients with refractory leukemia, three complete remissions (CRs) and one partial remission (13%) were observed in 30 patients with acute myeloid leukemia (AML).[5] In a subsequent phase II study, two CRs and one partial remission (18%) were observed in 16 patients with refractory AML.[6] Idarubicin, topotecan, and cytarabine (ara-C) are often included in combination regimens for patients with either previously untreated or relapsed myeloid leukemias.[9,10] A randomized phase I/II study was conducted to establish doses of troxacitabine given in combination with these agents.[4] Of 87 patients treated in this study, 74 patients had AML or advanced myelodysplastic syndrome (MDS). Of the patients with either AML or MD, 10 patients (13%) achieved CR and four patients (5%) had hematologic improvement. Six of 39 patients (15%) with refractory AML or MDS who received troxacitabine and ara-C (TA) achieved CR. Two of 18 patients (11%) with refractory AML or MDS who received troxacitabine and idarubicin (TI) achieved CR. On a recent analysis of first-line therapies in a cohort of 1,279 patients with AML or advanced MDS treated at the M.D. Anderson Cancer Center (Houston, TX) between 1991 and 1999, the idarubicin and ara-C (IA) regimen was at least equivalent, if not superior, to either fludarabine and ara-C or topotecan and ara-C regimens.[9] We thus conducted a prospective, randomized comparison of IA versus TA versus TI in patients aged 50 years or older with previously untreated AML and an adverse karyotype.

PATIENTS AND METHODS

Patient Eligibility

Patients aged 50 years or older with minimally pretreated (maximum of 3 days hydroxyurea and/or leukapheresis) AML were eligible if they had an abnormal karyotype other than inv(16), t(8;21), −Y, or –X. Patients were allowed to be randomly assigned treatment on the study before cytogenetic results were available if they had a blast count greater than 20×10^9/L, diffuse intravascular coagulopathy, or organ failure considered to be related to AML. Other eligibility criteria included serum bilirubin $\leq$ 2.0 mg/dL; AST or ALT levels less than 3 times the upper limit of normal or less than 5 times the upper limit of normal, if considered the result of leukemia; or

From the Department of Leukemia and the Department of Biostatistics, University of Texas M.D. Anderson Cancer Center, Houston, TX.

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Address reprint requests to Francis J. Giles, MD, Department of Leukemia, Box 428, University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030; email: frankgiles@aol.com.

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Table 1. Operating Characteristics of the Adaptive Randomization Design*

True Probabilities			*P* (choose arm 0 superior)‡	*P* (choose arm 1 superior)	*P* (choose arm 2 superior)	Mean Sample Sizes			
P_0	P_1	P_2†				n_0	n_1	n_2	Sum§
0.30	0.30	0.50	.025 (.005)	.178 (.145)	.797 (.740)	11	12	17	40
0.30	0.30	0.60	.020 (.007)	.118 (.097)	.862 (.843)	9	10	5	24
0.30	0.30	0.30	.101 (.029)	.449 (.321)	.450 (.333)	16	18	18	52
0.40	0.20	0.20	.540 (.299)	.238 (.102)	.230 (.102)	25	19	19	63
0.50	0.30	0.50	.209 (.157)	.154 (.114)	.637 (.564)	16	12	17	45
0.30	0.60	0.60	.005 (.004)	.507 (.501)	.488 (.478)	7	12	12	31

NOTE. Arm 0 = IA, arm 1 = TA, and arm 2 = TI.

Abbreviations: IA, idarubicin and cytarabine; TA, troxacitabine and ara-C; TI, troxacitabine and idarubicin.

*Data are based on 1,000 computer-simulated trials of each scenario.

†P_0, P_1, and P_2 are the true probabilities of response for arms 0, 1, and 2, respectively.

‡*P* (choose arm 0 superior) refers to the probability of choosing arm 0 as superior, on the basis of the interim analyses and the final analysis, given the indicated values of P_0, P_1, and P_2. The number in parentheses gives the probability of choosing arm 0 as superior and of stopping the trial based only on the interim analyses. The values for *P* (choose arm 1 superior) and *P* (choose arm 2 superior) are analogous to those for *P* (choose arm 0 superior).

§n_0, n_1, and n_2 are the mean sample sizes for arms 0, 1, and 2, respectively.

serum creatinine $\leq$ 1.5 mg/dL. The institutional review board approved the protocol, and all patients gave signed informed consent indicating that they were aware of the investigational nature of this study.

Treatment

Troxacitabine was supplied (Shire Pharmaceutical Development Ltd, Laval, Quebec, Canada) in vials containing 10 mg of lyophilized drug. The drug was diluted in the vial with 0.9% saline solution to obtain a 2 mg/mL stock solution. To yield the required dose, an appropriate volume of the stock solution was further diluted in a polyvinyl chloride infusion bag with 0.9% saline solution to a total volume of 50 mL, which was administered over 30 minutes. Patients were initially randomly assigned to one of three regimens at the following dosages: idarubicin 12 mg/m^2 intravenously (IV) daily for 3 days and ara-C 1.5 gm/m^2 IV over 2 hours daily for 3 days versus troxacitabine 6 mg/m^2 IV daily for 5 days and ara-C 1 gm/m^2 IV over 2 hours daily for 5 days versus troxacitabine 4 mg/m^2 IV daily for 5 days and idarubicin 9 mg/m^2 IV daily for 3 days. Patients who achieved CR received the first consolidation course, as per induction therapy, then subsequent cycles of the same regimen at reduced doses. Patients received trimethoprim and sulfa, or levofloxacin; fluconazole and itraconazole, or liposomal-encapsulated amphotericin; and valacyclovir as antimicrobial prophylaxis. Antibacterial and antifungal prophylaxis continued until neutrophil recovery was more than 0.5×10^9/L and antiviral prophylaxis continued for 2 weeks after patients began chemotherapy.

Response and Toxicity Criteria

CR was defined as normalization of the blood and bone marrow, with $\leq$ 5% blasts, normocellular or hypercellular bone marrow, neutrophil count $\geq 1 \times 10^9$/L, and platelet count $\geq 100 \times 10^9$/L. Toxicity was graded on a scale of 0 to 5, using National Cancer Institute common toxicity criteria Version 2.0.

Statistical Methods

Study design. Patients were assigned to one of three treatment arms in an adaptive randomized fashion.[11] Initially, the randomization was balanced, with a probability of 1 in 3 of random assignment to each of the three arms. As data accrued about efficacy, assignment probabilities shifted in favor of arms that were performing better.

The primary efficacy end point (success) was CR without nonhematologic grade 4 toxicity by 50 days. The comparison of arms in the data analysis and for the adaptive randomization was based on time to success, which we assumed was exponential, but which was truncated at 50 days. A priori we assumed that the median time to success, m_i, for each treatment followed an inverse gamma (2.001, 4.614) distribution.

The trial proceeded in the following manner. A maximum of 75 patients were to be randomized. Patients were to be randomly assigned to IA (arm 0), TA (arm 1), or TI (arm 2) with probabilities π_0, π_1, and π_2, respectively. Initially, $\pi_0 = \pi_1 = \pi_2 = 1/3$. The probability of random assignment to IA (π_0) remained as 1/3, as long as all three arms remained in the trial. When each new patient entered the trial, q_k, which was defined as $\Pr(m_k < m_0$ data), where $k = 1, 2$; and r, defined as $\Pr(m_1 < m_2$ data), were calculated to evaluate the stopping rules and to adapt the randomization probabilities. Although all three treatments remained in the trial, the randomization probabilities, π_1 and π_2, were calculated as $\pi_1 = (2/3)[q_1^2/(q_1^2 + q_2^2)]$ and $\pi_2 = (2/3)[q_2/(q_1^2 + q_2^2)]$. If at any time during the trial either $q_1 > 0.85$ or $q_2 > 0.85$ (ie, the current probability was at least 85% that TA or TI had a shorter time to CR than did IA), IA would be dropped from the randomization. If this were to happen and if both investigational arms were still in the trial, the randomization probability for arm 1, $\pi_1 = r^2/[r^2 + (1 - r^2)]$, and the probability of assignment to arm 2 would become $\pi_2 = 1 - \pi_1$. If at any time $q_1 < 0.15$ (ie, TA was being outperformed by IA) or $r < 0.15$ (ie, TA was being outperformed by TI), TA would be dropped from randomization. In addition, if $q_2 < 0.15$ (TI was being outperformed by IA) or if $r > 0.85$ (TI was being outperformed by TA), TI would be dropped from randomization. If at any time during the trial only IA and one investigational arm k remained, the randomization probability of arm q was set to $\pi_k = q_k^2/[q_k^2 + (1 - q_k^2)]$ and the randomization probability for the control was set to $\pi_0 = 1 - \pi_k$. Finally, an arm that dropped out could be reopened if information (ie, CR by day 49) became available from patients previously randomly assigned to that arm or if the other arms performed sufficiently poorly, subsequent to closure of the arm in question.

Before beginning the study, we used computer simulation to examine the performance of the above design (its operating characteristics) under various scenarios (Table 1). In particular, we were interested in the probability of (correctly) selecting an arm as superior to the other arms if it was truly superior, and conversely, the probability of (incorrectly) selecting an arm that was no better than the other arms. For example, assuming that the true probabilities of response with arms 0, 1, and 2 were 0.30, 0.30, and 0.50, respectively (Table 1, row 2), the overall probability of (correctly) choosing arm 2 (TI) as superior, on the basis of superiority shown both at interim analysis and at the end of the trial, was 0.797. The probability of (incorrectly) selecting arm 0 (IA) as superior was 0.025, whereas the probability of (incorrectly) selecting arm 1(TA) as superior was 0.178. The probability of stopping the trial early and declaring arm 2 superior was 0.740, whereas the corresponding probabilities for arms 0 and 1 were 0.005 and 0.145, respectively. In this scenario, the expected number of patients to be randomly assigned to arms 0, 1, and 2 were 11, 12, and 17, respectively. This contrasts with the numbers of patients (ie, 25, 25, and 25, respectively) that would pertain if no interim analyses had been done. Note in the above scenario that

despite the fact that IA and TA had the same true response rates, the probability of incorrectly selecting IA as the best arm is 0.005, whereas the probability of incorrectly selecting TA is 0.178. This indicates that the design was more protective of the investigational arms than of the standard arm (IA). This can be further appreciated by examining Table 1, row 4. Although all three arms here have the same true probability of response, the probability of (incorrectly) selecting arm 2 or 3 as superior is 0.899 (0.449 + 0.450). In sum, the design reflected our willingness to tolerate a relatively high probability of falsely declaring TA or TI superior (when they were not) to have a relatively high probability of selecting these arms when they were truly superior. This reflected the unsatisfactory response rate associated with the standard IA treatment arm. The methods used for logistic regression and for model criticism (goodness-of-fit analyses) were as previously described.[9]

RESULTS

Between the randomization dates of the first and last patients (April 3, 2001 and November 1, 2001, respectively), 34 patients were randomly assigned to treatment arms. Two of the 34 patients (9%) had a normal karyotype, but they were randomly assigned to treatment arms because their clinical condition did not permit waiting for cytogenetic results to become available and because of the probability that, given their ages (61 and 77 years), they would have abnormal cytogenetics. The 34 randomly assigned patients had a median age of 66 years (range, 50 to 78 years). Twelve patients (35%) had a Zubrod performance score of 2 or 3 at presentation. Eighteen patients (53%) had monosomies of chromosomes 5 and/or 7 or deletions of the long arms of these chromosomes (−5/−7); four patients had trisomy 8, 3, 11q deletions; seven patients had one or two miscellaneous abnormalities; and two patients were cytogenetically normal, as noted above. Thus, using the Medical Research Council classification system, 18 patients had a worse prognosis and 16 patients had an average prognosis, as determined by karyotype.[12] Fifteen patients (44%) had a documented abnormality in blood cell count for at least 1 month before diagnosis of AML presentation (antecedent hematologic disorder [AHD]), and in 10 of these patients the duration of AHD exceeded 3 months.

Table 2 lists the changes in randomization probabilities as the trial progressed. As noted above, the chance of randomization to IA remained 0.33 until either the TA or TI arm dropped out. The first patient was randomly assigned to arm TI. The second patient presented for random assignment 8 days later, and because the first patient had yet to achieve CR, there was a trivial increase in the probability of assignment to TA (0.34) rather than to TI (0.32), with the probability of assignment to IA remaining at 0.33. The first patient was assigned to TA on June 6, 2001. By this time, the success rates were one of two patients with IA and zero of two patients with TI (CR in patient 1 occurred on day 50), whereas in an additional three patients given IA and in an additional two patients given TI, responses remained unknown (at days 31, 35, and 45 in the IA group and at days 9 and 21 in the TI group). This led to probabilities of randomization to IA, TA, and TI of 0.33, 0.42, and 0.24, respectively. When patient 25 presented for randomization on September 12, 2001, success rates were five of nine patients (55%) with IA, three of seven patients (43%) with TA, and zero patients with TI. Responses were unknown at days 21 and 12 in patients 23 and 24, respectively, who were given IA and at day 44 in patient 20, who was given TA. At this time, the probability of random assignment to TI became 0.0 (ie, the TI arm dropped out), whereas the probability of random assignment to IA became 0.87, and probability of random assignment to TA became 0.13. The final patient (ie, patient 34) was randomly assigned to treatment on November 1, 2001. At this time, success rates were seven of 12 patients (58%) with IA, three of eight patients (37%) with TA, and zero of five patients with TI. Responses remained unknown at days 27, 23, 22, 9, and 3 in patients 28, 29, 30, 31, and 33, respectively, who were given IA; and at days 39 and 30 in patients 26 and 32, respectively, who were given TA. The probabilities of random assignment were 0.96 for IA and 0.04 for TA, and the TA arm was dropped. Because success was defined as CR without nonhematologic grade 4 toxicity by 50 days, the final success rates were 10 of 18 patients (55%) with IA, three of 11 patients (27%) with TA, and zero of five patients with TI.

Two CRs occurred after day 49 in the TA group (patients 11 and 26) and one CR occurred in the TI group (patient 1). Accordingly, the final CR rates were 10 of 18 patients (55%) with IA, five of 11 patients (45%) with TA, and one of five patients with TI. Using a beta distribution with a noninformative prior (0.5,0.5),[13] the probability, given these data, that the CR rate would be lower with TA than with IA was 70%; the probability that the CR rate would be 20% higher with TA than with IA was 5%. Corresponding values for TI were 92% and 1%.

Among patients achieving CR, recurrence rates by treatment arm were seven of 10 patients (70%) with IA, four of five patients (80%) with TA, and one of one patient (100%) with TI. For IA, times to relapse were 6, 10, 11, 12, 25, 32, and 52 weeks, with remissions ongoing in three patients at 15, 15, and 34 weeks. Corresponding times for TA were 19, 21, 22, and 40 weeks, with one remission ongoing at 46 weeks; the only patient achieving CR after TI relapsed 12 weeks later. No patient died in CR. Therefore, there was no significant difference among patients receiving IA, TA, and TI in terms of time to treatment failure (relapse or death in CR).

A fundamental reason to distinguish between CRs occurring before the start of therapy and those occurring 49 days after the start of therapy is the hypothesis that the latter are essentially cosmetic (see Discussion). Disease reappeared (at 22 and 40 weeks from CR date) in both patients who achieved CR after more than 49 days from the start of TA therapy; however; there were no differences in time to treatment failure between patients given TA who took less than 50 days to achieve CR and patients who took more than 50 days to achieve CR. All patients who achieved CR with IA therapy did so within 49 days after starting therapy. The only CR with TI occurred 50 days after beginning therapy. All of the above results suggest that there are too little data to test the hypothesis of cosmetic CR in this study. Death rates were 11 of 18 patients (61%) with IA, seven of 11 patients (64%) with TA, and five of five patients (100%) with TI. Time to death was equivalent in all three regimens. The failure of the higher CR rate with IA to translate into a superior survival, even when compared with TI, seems attributable to the brevity of the IA-induced CR.

The number of patients randomly assigned to treatment was sufficiently small that imbalances in the distribution of important

Table 2. Application of Adaptive Randomization Design

Patient	Probability of Assignment to IA (arm 0)	Probability of Assignment to TA (arm 1)	Probability of Assignment to TI (arm 2)	Treatment Arm Assigned (assignment date)	Outcome
1	.333333	.333333	.333333	TI (4/3/01)	CR day 50
2	.333333	.343163	.323507	IA (4/11/01)	CR day 35
3	.333333	.348964	.317706	TI (4/16/01)	Resistant day 24
4	.333333	.366816	.299854	IA (4/24/01)	Resistant day 50
5	.333333	.383675	.282995	IA (5/3/01)	Resistant day 60*
6	.333333	.389663	.277007	IA (5/7/01)	CR day 32
7	.333333	.39438	.27229	IA (5/11/01)	Died day 19*
8	.333333	.438409	.228261	TI (5/17/01)	Resistant day 50
9	.333333	.465855	.200815	TI (5/29/01)	Resistant day 45
10	.333333	.426485	.240185	TA (6/6/01)	CR day 42
11	.333333	.497798	.168872	TA (6/28/01)	CR day 53*
12	.333333	.49508	.17159	TA (7/6/01)	Resistant day 75*
13	.333333	.46556	.20111	TA (7/16/01)	Resistant day 41
14	.333333	.566989	.99681	TI (7/19/01)	Resistant day 38
15	.333333	.565015	.101655	TA (7/21/01)	CR day 27
16	.333333	.560204	.106466	IA (7/23/01)	Resistant day 20
17	.333333	.558311	.108359	TA (7/24/01)	CR day 28
18	.333333	.553227	.113443	TA (7/26/01)	Resistant day 39
19	.333333	.536498	.130172	TA (7/31/01)	Resistant day 55*
20	.333333	.527337	.139333	IA (8/1/01)	CR day 33
21	.333333	.489902	.176768	IA (8/8/01)	CR day 24
22	.333333	.459059	.207611	IA (8/14/01)	CR day 26
23	.333333	.576503	.090167	IA (8/23/01)	CR day 33
24	.333333	.594821	.071849	IA (8/31/01)	CR day 30
25	.870782	.129218	0	IA (9/12/01)	Died pretreatment†
26	.872424	.127576	0	TA (9/24/01)	CR day 72*
27	.9564	.0436	0	TA (10/2/01)	Resistant day 55*
28	.959345	.040655	0	IA (10/5/01)	CR day 34
29	.959345	.040655	0	IA (10/9/01)	Resistant day 30
30	.959345	.040655	0	IA (10/10/01)	CR day 38
31	.957311	.042689	0	IA (10/23/01)	Resistant day 29
32	.957311	.042689	0	TA (10/23/01)	Resistant day 46
33	.955233	.044767	0	IA (10/29/01)	Resistant day 31
34	.95925	.04075	0	IA (11/1/01)	CR day 25

Abbreviations: IA, idarubicin and cytarabine; TA, troxacitabine and ara-C; TI, troxacitabine and idarubicin; CR, complete response.

*For purposes of random assignment of subsequent patients to treatment, response in these patients was considered to have occurred on day 50 (see text).

†This patient was randomized on 9/12/01 and died 12 days later without having received treatment because of intercurrent problems; for purposes of random assignment of subsequent patients to treatment, this patient was considered to have experienced treatment failure on day 12.

prognostic covariates between treatment arms could have arisen. Thus, the IA group tended to have somewhat poorer performance status, but more favorable cytogenetics than the TA or TI groups. The IA group also had an AHD less frequently and they were more frequently treated in HEPA-filtered rooms (Table 3). Given these data, logistic regression was performed to determine whether a treatment effect was present after accounting for covariates not related to treatment. Two considerations motivated our approach. First, there were too few patients for which to examine the independent effects of all the covariates shown in Table 3.[14,15] Second, as noted in the discussion of the study design, we wished not to reject TA or TI, even at the expense of rejecting IA. These desiderata led us to examine the following for inclusion in a logistic model predicting CR (at any time): treatment arm (IA *v* TA *v* TI), cytogenetics ($-5/-7$ or complex *v* other), and AHD (no *v* yes). Table 3 shows that the IA group was better than the TA group (with respect to cytogenetics and AHD) and than the TI group (with respect to AHD). In contrast, performance status (less favorable in IA patients) and age (similar in IA, TA, and TI groups) was not considered for inclusion. The fitted model (Table 4) indicates that treatment with IA (rather than TA), TA (rather than with TI), and cytogenetics (other than the $-5/-7$ or complex) were independent predictors of CR, but that none achieved statistical significance (ie, $P < .05$).

DISCUSSION

Induction therapy for AML is unsatisfactory, particularly for elderly patients and/or for those with an adverse karyotype.[9] Troxacitabine is a novel nonnatural nucleoside analog with significant activity as a single agent in patients with refractory AML.[5-7] On a phase I/II randomized study, troxacitabine combined with ara-C or idarubicin achieved CR in patients with refractory AML, including patients who had failed prior high-

Table 3. Distribution of Covariates According to Treatment Arm

	IA (n = 18)	TA (n = 11)	TI (n = 5)
Age, years			
Median	67	65	65
25th and 75th percentiles	61, 76	61, 70	63, 68
Performance status			
Zubrod 3	2	0	0
Zubrod 2	6	3	1
Cytogenetics −6/−7 or complex	9	7	2
Cytogenetics normal	2	0	0
AHD	5	7	3
Treated in HEPA-filtered room	10	3	3

Abbreviations: IA, idarubicin and cytarabine; TA, troxacitabine and ara-C; TI, troxacitabine and idarubicin; AHD, antecedent hematologic disorder.

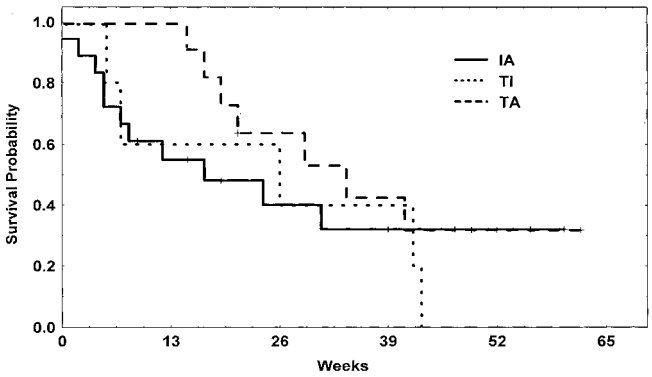

Fig 1. Survival of patients treated with idarubicin and cytarabine (ara-C; IA), troxacitabine and ara-C (TA), or troxacitabine and idarubicin (TI).

dose ara-C.[4] We thus conducted a prospective, randomized study of these troxacitabine-based regimens versus IA in an elderly cohort of patients with poor prognosis AML. In terms of early CR, IA was superior to both troxacitabine combinations. When CRs are compared at any time, it seems unlikely that TA would be superior to IA in these patients. Overall survival with all three study regimens was equivalent (Fig 1). Randomization in this study was carried out in an adaptive Bayesian fashion.[13] This randomization process was used in an attempt to align two somewhat conflicting major issues (ie, the reluctance of investigators to randomly assign patients to standard or control regimens that were known to be highly unsatisfactory and the demand for truly randomized studies to generate plausible data) in the conduct of randomized studies in patients with AML.

Some elaborations are necessary. First, we addressed the possibility that the statistical design prevented us from identifying the activity of the TA or TI regimens by computing the design's operating characteristics (Table 1). As noted, the design was intentionally more protective of TA and TI than of IA. Furthermore, the design allowed us to reach a conclusion after treating 34 patients. Equally important, as a result of the adaptive randomization, 18 patients (53%) in the study received the seemingly superior IA regimen, whereas only 11 patients (33%) would have received this regimen if random assignment to treatment had not been done adaptively.

An important issue is what is meant by superiority. In particular, was it reasonable to use CR obtained by day 50 of course 1 as the criterion of success? Our rationale in defining success in this way was two-fold. First, it is well known that most remissions attained only after a second course of induction therapy are transient.[16] Second, we have observed that subsequent survival in patients who are in CR after one course (but who require > 49 days to do so) more closely resembles that seen in patients who live at least 49 days (but never achieve CR) than that seen in patients who are in CR by day 49 of first-induction therapy.[17] Thus, CR attained in course 2 or only after 49 days of a first-induction course have been cosmetic, motivating the criterion chosen here. It can be contended, however, that this formulation derives from data in patients given IA and that it may not be applicable to regimens, including novel agents, such as troxacitabine. As noted above, there is insufficient information to examine this possibility in this study. However, when all CRs achieved at any time are included in the analysis, it still seems unlikely that TA or TI are superior to IA in the patient population with AML studied in this protocol. The survival data (Fig 1) lend support to this view.

Another difficulty stems from the possibility of imbalances in the distribution of important prognostic covariates (Table 3). This difficulty stems from the small number (n = 34) of patients randomized. Even though there was no suggestion that TA or TI produced higher CR rates than IA, even when the analysis was done in a manner that might have been expected to favor the former regimens (Table 4), there still may have been imbalances in latent unobserved covariates. Whether this possibility, which is inherent in any adaptively randomized design, is sufficient to outweigh the medical advantages consequent to the use of adaptive randomization may vary depending on circumstances.

Finally, it should be emphasized that these data do not address the relative efficacy of troxacitabine-based regimens in other important subsets of patients with either de novo or relapsed AML. In vitro data indicate that troxacitabine has activity against ara-C–resistant tumor cells.[18-20] Troxacitabine, either as a single agent or when combined with ara-C, has activity in patients with AML who have failed high-dose ara-C therapy.[7] Thus, troxacitabine-based regimens merit further investigation in the relapsed AML setting. However, within the limits discussed above, IA remains the least unsatisfactory induction regimen we have investigated to date in elderly patients with adverse karyotype AML.

Table 4. Logistic Regression Model for CR

Covariate	Regression Coefficient*	Standard Error	P
Cytogenetics = −5/−7 or complex rather than other	−1.4029	0.7742	.07
Treatment IA rather than TA	0.7219	0.5558	.19
Treatment TI rather than TA	−1.1945	0.8367	.15

Abbreviations: IA, idarubicin and cytarabine; TA, troxacitabine and ara-C; TI, troxacitabine and idarubicin; CR, complete response.

*A negative value indicates that the covariate has an unfavorable independent effect on the probability of CR; a positive value denotes the converse.

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