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A phase III comparison of high dose ARA-C (HIDAC) versus HIDAC plus mitoxantrone in the treatment of first relapsed or refractory acute myeloid leukemia Southwest Oncology Group Study☆

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Abstract

The aim of this study is to determine whether the addition of mitoxantrone to high dose cytarabine improves the outcome of treatment in patients with relapsed or refractory acute myeloid leukemia (AML). One hundred and sixty-two eligible patients, 14–76 years of age, with AML either in first relapse or that failed to respond to initial remission induction therapy, with no CNS involvement were randomized to receive therapy with cytarabine 3 gm/M^2 IV over 2 h every 12 h for 12 doses on days 1–6 (Arm I) (HIDAC); or HIDAC plus mitoxantrone 10 mg/M^2 IV daily on days 7–9 (Arm II) (HIDAC + M). Patients achieving complete remission were treated with three courses of consolidation including HIDAC (Ara-C 3 gm/M^2 IV q 12 h days 1–3; 2 gm/M^2 over age 50) alone (ARM I) or with mitoxantrone (10 mg/M^2 IV day 1) (ARM II). Among 162 patients (81 HIDAC, 81 HIDAC + M) evaluated for induction toxicity, there were 10 (12%) induction deaths with HIDAC and 13 (17%) with HIDAC + M (2-tailed $P = 0.65$). Most early deaths were due to infection and/or hemorrhage. Among 162 patients evaluated for responses to induction therapy, 26/81 (32%) HIDAC and 36/81 (44%) HIDAC + M patients achieved complete remission (two-tailed $P = 0.15$). Although this difference was not statistically significant in univariate analysis, it was after adjusting for the effects of WBC and PMN percentage in multivariate analysis ($P = 0.013$). Median survivals from study entry were 8 months (HIDAC) and 6 months (HIDAC + M); 2-tailed logrank $P = 0.58$. Among 48 patients registered for consolidation, the median disease-free survivals from that registration were 8 months with HIDAC and 11 months with HIDAC + M ($P = 0.60$). There were three treatment-related deaths during consolidation (1 HIDAC, 2 HIDAC + M), all due to infections. In this randomized trial, the addition of mitoxantrone to high-dose cytarabine was associated with a trend toward a higher CR rate. There was less evidence for an advantage in disease-free or overall survival, although any such conclusion is limited by the size of the study.

Keywords: High dose ARA-C; Mitoxantrone; Acute myeloid leukemia

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1. Introduction

High dose cytarabine (HIDAC) either alone or in combination with anthracyclines is active in the treatment of AML inducing remission in 50–81% of patients with previously untreated disease and in up to 50% of patients with recurrent leukemia [1–7]. It is uncertain whether the addition of a second agent to HIDAC increases complete remission rates and/or disease-free survival in relapsed or refractory AML. The Southwest Oncology Group therefore initiated a study, SWOG-8326, to evaluate the impact of mitoxantrone when used in combination with high dose cytarabine in the therapy for acute myeloid leukemia in first relapse or primary induction failure.

2. Patients and methods

Between May 1985 and May 1992, 210 patients with acute myeloid leukemia (AML) were registered onto study SWOG-8326. Eligibility criteria included having AML in first relapse or having failed to achieve a complete remission after one or more cycles of initial induction therapy. At least 14 days must have had elapsed since completion of previous chemotherapy and patients must have had recovered from any side effects or active infection at the time of registration. Those with prior exposure to HIDAC therapy were excluded from the study. Patients were required to have a performance status between 0 and 2 by SWOG criteria or Karnofsky score $>60\%$. They must have had normal left ventricular function as determined by multiple-gated angiogram (MUGA) scan, normal renal function with creatinine <1.5 mg% and serum bilirubin <2 mg% and SGOT and SGPT $<4\times$ normal. Patients with significant prior medical illness or another prior malignancy were excluded. All patients provided written informed consent.

The diagnosis was made at the treatment institutions based on bone marrow aspirates stained with Wright or Wright–Giemsa, periodic acid-Schiff (PAS), nonspecific esterase and peroxidase or Sudan Black stains. Bone marrow aspirate and biopsy slides were reviewed by the Leukemia Pathology Committee of the Southwest Oncology Group.

The study design is shown schematically in Fig. 1. Patients were randomized without stratification to receive induction therapy with single agent high dose cytarabine (HIDAC) 3 gm/M^2 intravenously (IV) over 2 h every 12 h for 12 doses on days 1–6 (Arm I), or HIDAC plus mitoxantrone 10 mg/M^2 IV daily on days 7–9 (Arm II). The dose of HIDAC was reduced to 2 gm/M^2 for patients over 50 years old. A second course of induction therapy was given if the day-14 bone marrow was hypocellular or normocellular with blasts and promyelocytes between 10 and 25%. Patients were taken off protocol treatment if the day-14 marrow showed $>25\%$ blasts and promyelocytes and no change in cellularity, if they did not achieve a remission marrow after two cycles of induction therapy, or if they suffered a relapse after achieving complete or partial remission. Patients achieving complete remission (CR) were continued on the same drugs for three courses of consolidation: HIDAC 3 gm/M^2 IV q 12 h on days 1–3 (2gm/M^2 over age 50) with (ARM II) or without (ARM I) mitoxantrone 10 mg/M^2 IV day 1. Patients were not given maintenance therapy after completion of the three consolidation courses.

Pretreatment evaluation included cardiac evaluation with MUGA scan, bone marrow aspiration and biopsy, complete blood count, urinalysis, renal and hepatic functions, chest X-ray, EKG, and spinal tap. Bone marrow aspiration and biopsy were performed on days 14 and 28 of induction therapy and repeated when blood counts recovered to document a remission marrow. After complete remission was obtained, bone marrow aspiration and biopsies were repeated prior to each course of consolidation therapy and every 3 months for the first 2 years.

There were no dosage modifications for hematologic toxicity. Subsequent courses of therapy were postponed until recovery if patients suffered Grade I, II or III nonhematologic toxicity. Cytarabine was discontinued and patients removed from the study in the presence of grade III or IV hepatic or CNS toxicity.

Complete remission was defined as a bone marrow with less than 10% of the sum of blasts and promyelocytes with normal appearing erythroid, myeloid and megakaryocytic precursors (both quantitative and qualitative). Circulating granulocytes were required to be >1000/cu.mm. and platelets $>100\,000$/cu.mm.

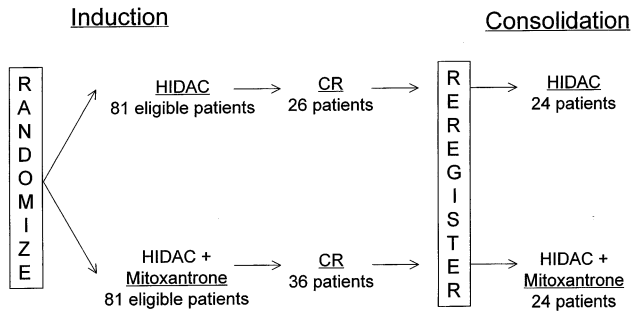

Fig. 1. Schematic description of study design and patient flow. The numbers of eligible patients randomized, the numbers achieving complete remission, and the numbers registered for consolidation therapy are shown.

There could be no evidence of leukemic infiltration on physical findings. Other results were considered no response.

3. Statistical considerations

This study was originally designed as a randomized comparison of three intensive regimens HIDAC, HIDAC + mitoxantrone and HIDAC + AMSA. In June 1988 the study's Data Monitoring Committee (DMC) closed the HIDAC and AMSA arm due to excessive toxicity without evidence of aufficient compensating benefit. At the time of that analysis, with between 55 and 63 patients randomized to each arm, the incidence of fatal toxicity during induction was 29% in the HIDAC + AMSA arm compared to 7% in the HIDAC arm and 11% in the HIDAC + mitoxantrone arm [8]. The majority of early deaths in the HIDAC + AMSA arm were due to infections. The DMC then set an accrual goal of 172 eligible patients for the HIDAC and HIDAC + mitoxantrone arms. This number of patients, accrued over 3.25 years and with one additional year's follow-up, would provide the following levels of statistical power for two-tailed tests at critical level $\alpha = 0.05$; 0.89 to detect the difference between CR rates of 40% and 75%; 0.86 to detect a hazard ratio of 1.67 in the analysis of survival (assuming median survival of 8 months with HIDAC); and 0.85 to detect a hazard ratio of 2.0 in the analysis of RFS (assuming 98 patients with CR and median RFS of 38 weeks with HIDAC). An interim analysis in April 1992 demonstrated no significant difference between HIDAC and HIDAC + mitoxantrone arms with respect to CR rate (based on 149 evaluated patients) or survival (160 patients). Additional analyses demonstrated that completion of accrual to 172 eligible patients would almost certainly not modify these conclusions. Based on these interim results the DMC decided to close the study.

Overall survival was measured from the day of randomization (i.e. entry into the study) until death from any cause, with observation censored at the day of last contact for patients not known to have died. Relapse-free survival (RFS) was measured from the day CR was established until relapse or death from any cause, with observation censored at the day of last contact for patients without report of relapse or death. For patients entered on the consolidation portion of the study, survival and disease-free survival (DFS) were measured to the same endpoints, but from the day of consolidation registration. Rates of complete response (CR) and toxicity were compared between the two treatment arms by means of exact tests calculated using the commercially available StatXact-Turbo program (Cytel Software Corporation, Cambridge MA, 1992). Distributions of survival, RFS, and DFS were estimated by the method of Kaplan and Meier [9] and compared between treatment arms using the log rank test [10]. Further analyses of the effects of treatment and other factors were based on logistic regression models for CR rate and proportional hazards regression models for survival and RFS [11,12]. Quantitative characteristics such as age and blood counts were treated as continuous variables in these regression analyses. Results of statistical tests are represented by two-tailed P-values. This report is based on data available October 25, 1998.

4. Results

4.1. Patients

A total of 210 patients were randomly assigned to HIDAC or HIDAC + mitoxantrone between June 1985 and May 1992. Forty-eight (23%) of these patients were ineligible, mainly due to failure to meet central pathology review criteria. The results presented here are based on these 162 fully eligible patients, as called for in the study's original design and the recommendations of the data monitoring committee. Additional analyses based on all 210 randomized patients were also performed; the result of these intent-to-treat analyses, were very similar to those reported here and are not presented. Characteristics of the 162 eligible patients (81 HIDAC, 81 HIDAC + mitoxantrone) are summarized in Table 1. The two treatment arms were generally comparable with respect to the variables in Table 1, although there were some differences. The median age of the HIDAC + mitoxantrone patients was 5 years greater than that of the HIDAC patients, and the median WBC count and PMN percentage of the HIDAC + mitoxantrone patients were 0.3 more and 6 percentage points less, respectively, compared to HIDAC patients. Overall about two-thirds of the patients were in relapse after achieving remission while the rest were refractory to initial induction therapy.

4.2. Induction toxicity

One HIDAC + mitoxantrone patient refused to receive protocol treatment and was therefore excluded from the analysis of toxicity. There were eight (10%) induction deaths among the 81 eligible HIDAC patients, compared to 13 (16%) among the 80 eligible HIDAC + mitoxantrone patients (two-tailed $P = 0.25$). These deaths were primarily due to infection (16) or hemorrhage (3). Five (6%) HIDAC and 11(14%) HIDAC + M patients had fatal infections ($P = 0.12$). Neurologic toxicity of grade 3 or higher occurred in six (7%) HIDAC and two (3%) HIDAC + mitoxantrone patients ($P = 0.28$). Grade 3 + mucositis occurred in no HIDAC patients and five (6%) HIDAC + mitoxantrone

Table 1
Patient and disease characteristics

	HIDAC ($n = 81$)		HIDAC + mitoxantrone ($n = 81$)	
	Median (or number)	Range (or percent)	Median (or number)	Range (or percent)
Age	48	14–75	53	18–76
Sex M/F	49/32	60/40%	42/39	52/48%
Race B/W/Other	7/71/3	9/88/4%	11/66/4	14/81/5%
BM Blasts (%)	57	0–98	68	0–95
Hemoglobin (mg/dl)	10.9	4.7–16.1	10.6	5.8–15.3
Platelets (1000/ul)	69	10–552	73	7–573
WBC at diagnosis(1000/ul)	5.2	0.4–108.6	5.5	0.5–177.0
Absolute Blasts (1000/uL)	0.3	0–90.4	0.6	0–117.0
Absolute PMNs (1000/ul)	0.7	0–16.3	1.0	0–93.8
FAB CLASS (Central Review)				
M1	26	32%	19	23%
M2	35	43%	38	47%
M3	3	4%	4	5%
M4	3	4%	9	11%
M5	5	6%	6	7%
M6	4	5%	1	1%
M7	0	0%	1	1%
M0	1	1%	1	1%
Myeloid, NOS	4	5%	2	2%
Disease status				
Relapsed	54	67%	52	64%
Refractory	27	33%	29	36%

patients ($P = 0.028$). Diarrhea of any grade occurred in 15 (19%) HIDAC and 25 (31%) HIDAC + mitoxantrone patients ($P = 0.070$). Eight patients were removed from induction therapy because of toxicity, three in each treatment arm due to neurotoxicity and two other HIDAC + mitoxantrone patients due to cardiac toxicity and small bowel obstruction.

4.3. Induction treatment outcomes

All 162 eligible patients were evaluated for response to treatment and 62 achieved complete responses: 26 (32%; 95% confidence interval [C.I.] 22–43%) on HIDAC and 36 (44%; 95% C.I. 33–56%) on HIDAC + mitoxantrone (Table 2). These CR rates were not significantly different in a univariate comparison (two-tailed $P = 0.15$). Additional analyses of CR rates were performed to investigate the effects of adjusting for the patient and disease characteristics listed in Table 1. In simple logistic regression analyses several factors were found to have statistically significant prognostic effects: the CR rate increased with decreasing WBC ($P = 0.0001$), peripheral blast percentage ($P = 0.0018$) and absolute peripheral blast count ($P = 0.0003$) and with increasing PMN percentage ($P = 0.0067$) and peripheral lymphocyte percentage ($P = 0.0086$). Several marginally significant beneficial prognostic factors were also identified: lower marrow blast percentage ($P = 0.034$); marrow promyelocyte percentage ($P = 0.071$); higher hemoglobin ($P = 0.067$); higher platelet count ($P = 0.081$); and absence of myelocytes in the peripheral blood ($P = 0.011$). Of course, many of these variables are highly correlated with each other, and consequently in multiple regression analysis only two factors retained independent prognostic significance: the CR rate increased with decreasing WBC ($P = 0.0003$); and increasing PMN percentage ($P = 0.047$). As shown in Table 1, the HIDAC + mitoxantrone patients tended to have somewhat higher WBC and lower PMN percentages; i.e. a poorer prognosis for response than the HIDAC patients. As a result, the unadjusted comparison of treatment arms tended to understate the significance of the difference. After adjusting for the effects of WBC and PMN percentage in multiple logistic regression analysis, the treatment difference appeared to be at least marginally statistically significant ($P = 0.013$) in favor of the HIDAC + mitoxantrone arm. Table 3 displays CR rates among subsets of patients defined by WBC and PMN percentage. In three of the four subsets, the CR rate with HIDAC + mitoxantrone is at least 20 percentage points higher than with HIDAC. Although the HIDAC CR rate was higher in the fourth subset (WBC > 5.0 and PMN > 15%), the treatment difference did not vary significantly among the four subsets ($P = 0.43$).

Estimated distributions of overall survival from the day of entry on study are shown in Fig. 2. Of the 162 eligible patients, 151 died. Except for one patient lost to

follow-up after 11 months, the remaining 11 were last known to be alive between 5.2 and 11.3 years after study entry (median 9.2 years). As shown in Table 2, the estimated median duration of survival was 8 months (95% C.I. 5–9 months) with HIDAC and 6 months (95% C.I. 5–8 months) with HIDAC + mitoxantrone (two-tailed logrank $P = 0.94$). The estimated mortality hazard ratio (HIDAC + mitoxantrone relative to HIDAC) was 0.99 (95% C.I. 0.72–1.36 months). Several significantly beneficial prognostic factors for survival were identified in simple proportional hazards regression analyses: lower WBC ($P = 0.0030$); lower marrow blast percentage ($P = 0.0021$); peripheralblast percentage ($P = 0.0002$) or count ($P = 0.0006$); absence of peripheral promyelocytes ($P = 0.0011$) or myelocytes ($P = 0.0040$); higher hemoglobin ($P = 0.0064$); and PMN percentage ($P = 0.0072$). Marginally significant beneficial prognostic factors included: lower marrow promyelocyte percentage ($P = 0.093$); higher lymphocyte percentage in the marrow ($P = 0.014$) or peripheral blood ($P = 0.018$); and higher platelet count ($P = 0.033$). In multiple regression analysis, however, only two factors retained independent prognostic significance: survival increased significantly with decreasing peripheral blast percentage ($P = 0.0004$) and was significantly poorer for patients with promyelocytes present in the peripheral blood ($P = 0.0020$). After adjusting for the effects of these factors, the treatment difference remained nonsignificant ($P = 1.00$). The adjusted estimate of the mortality hazard ratio was 1.00 (95% C.I. 0.07–1.42 months).

Relapse-free survival (RFS), measured from the day CR was established, was analyzed for the 62 patients who achieved CR (Fig. 3). Forty-seven of these patients relapsed, and nine others died without relapsing primarily due to toxicities of induction (one patient), consolidation (three patients) or bone marrow transplantation (four patients). The ninth patient died of lung cancer. The other six remained alive in remission between 7.6 and 11.2 years (median 9.3 years). As shown in Table 2, the estimated median duration of RFS was 9 months (95% C.I. 4–11 months) with HIDAC and 5 months (95% C.I. 3–7 months) with HIDAC + mitoxantrone ($P = 0.30$). The estimated hazard ratio for relapse or death was 1.33 (95% C.I. 0.78–2.27 months). In simple regression analyses only two marginally significant prognostic factors were identified, and both retained independent marginal significance in multivariate analysis. RFS increased with increasing pretreatment hemoglobin ($P = 0.045$) and was significantly better for patients with no peripheral metamyelocytes ($P = 0.037$). The treatment difference remained nonsignificant after adjusting for the effects of these two factors ($P = 0.63$). The adjusted estimate of the hazard ratio was 1.16 (95% C.I. 0.64–2.11 months).

4.4. Consolidation

Of the 62 patients (26 HIDAC, 36 HIDAC + mitoxantrone) who achieved CR, 14 (2 HIDAC,12 HIDAC + mitoxantrone) were not registered for protocol consolidation therapy. Five of these (including both HIDAC patients) received bone marrow transplantation in remission. The other nine HIDAC + mitoxantrone patients were removed from protocol treatment for medical reasons (3), refusal (3), early relapse (1), or protocol error (2). The remaining 48 patients included 92% of the HIDAC patients who achieved CR, but only 67% of the HIDAC + mitoxantrone patients. Three infection deaths were attributed to consolidation toxicity (one HIDAC, two HIDAC + mitoxantrone).

Table 2
Treatment outcomes

	HIDAC		HIDAC + mitoxantrone	
	Number or estimate	Conf. Int.[a]	Number or estimate	Conf. Int.[a]
Induction				
Eligible patients	81		81	
Complete response (%)	32	22–43	44	33–56
Overall survival(median, in months)[b]	8	5–9	6	5–7
Relapse–free survival (median, in months)[c]	9	4–11	5	3–7
Consolidation				
Eligible patients	24		24	
Survival(median, in months)[d]	11	7–20	11	6–21
Disease–free survival(median, in months)[d]	8	4–10	11	2–12

[a] Conf. Int. = 95% confidence interval
[b] Overall survival measured from day of randomization.
[c] Relapse-free survival measured from day CR established.
[d] Survival and disease-free survival measured from day of registration for consolidation.

Table 3
Response to treatment by WBC count and PMN percentage

WBC	Treatment arm	PMN ≤ 15%		PMN > 15%	
		CRs/Pts	%CR	CRs/Pts	% CR
≤5.0	HIDAC	2/12	17%	13/26	50%
	HIDAC + mitoxantrone	7/17	4 1%	16/23	70%
>5.0	HIDAC	2/20	10%	7/17	41%
	HIDAC + mitoxantrone	8/24	33%	5/17	29%

No other fatal toxicities were reported. Seven (29%) of the 24 HIDAC + mitoxantrone patients were removed from consolidation treatment early due to toxicity (neurologic in three patients and hepatic, cardiac, infection, and platelet refractoriness in one each). In contrast, none of the 24 HIDAC patients was removed from treatment due to toxicity. As shown in Table 2, the two treatment arms had similar median durations of overall and disease-free survival (both measured from the day of registration for consolidation therapy). However, the number of consolidation patients is too small and the HIDAC + mitoxantrone patients were more highly selected than the HIDAC patients, so it is not possible to draw any firm conclusion about the relative effficacy of adding mitoxantrone to consolidation therapy.

5. Discussion

Despite high response rates following initial induction therapy with standard dose cytarabine and anthracycline, more than half of AML patients will relapse. This study showed a higher complete remission rate with HIDAC + mitoxantrone (44%) than with HIDAC (32%) for induction chemotherapy in patients with AML in first relapse. Although this difference was not statistically significant ($P = 0.15$), patients in the HIDAC + mitoxantrone arm had higher WBC count and lower PMN percentages, which were detrimental prognostic factors for response. After adjusting for the effects of WBC and PMN percentages in the multiple logistic regression analysis, the treatment difference appeared to be marginally significant ($P = 0.013$). Although this suggests that HIDAC + mitoxantrone might produce a higher CR rate than HIDAC alone, there was less evidence of a corresponding benefit in survival or RFS. The frequencies of induction death, infection, neurologic toxicities and diarrhea did not differ significantly between the two treatment groups.

However, the incidence of grade 3 mucositis seemed to be higher in the group receiving HIDAC + mitoxantrone ($P = 0.028$). Fewer patients who received HIDAC + mitoxantrone went on to protocol-directed consolidation therapy. Moreover, among those who did go on, more HIDAC + mitoxantrone patients were removed early from consolidation due to toxicities.

Bone marrow cytogenetic studies and flow cytometry, important prognostic factors for response rate and outcome in untreated AML, were not included in the analyses, since the tests were not routinely obtained during the first several years of the study, nor were assays of multi-drug resistance available. Thus, we were unable to determine whether these factors might identify subgroups of patients who particularly benefited from the addition of mitoxantrone.

Based on the results of this study, the choice of whether to add mitoxantrone to HIDAC for AML reinduction may depend on the goals of reinduction therapy. If the goal is to achieve a second remission so that the patient can go on to other potentially curative therapy, for example, marrow transplantation, then adding mitoxantrone may be indicated since the CR rate with the combination tended to be higher than with HIDAC alone even though there seems to be more induction toxicity in the combination arm. Larson et al. reported a higher remission rate when AMSA was added to HIDAC if there were inadequate cytoreduction by day 6 for the treatment AML in first relapse. The fractional reduction of leukemic cells in the day 6 bone marrow aspirate and biopsy were the strongest predictors of achieving remission [13]. If, however, reinduction therapy is being administered with the goal of prolonging survival on its own, there is less evidence from this study that mitoxantrone adds to the overall effectiveness of HIDAC. The strength of this conclusion is weakened, however, by the size of the study. For those achieving second remission, significantly longer leukemia free survival can be obtained with HLA-identical sibling transplant rather than consolidation chemotherapy, especially for those younger than 30 years old and with first complete remissions longer than 1 year (41% versus 17%, $P = 0.017$) [14]. Duration of the first remission longer than 12 months and favorable cytogenetic study also predicts long term leukemia free survival with a second continuous complete remission rate of 24% at 5 years [15].

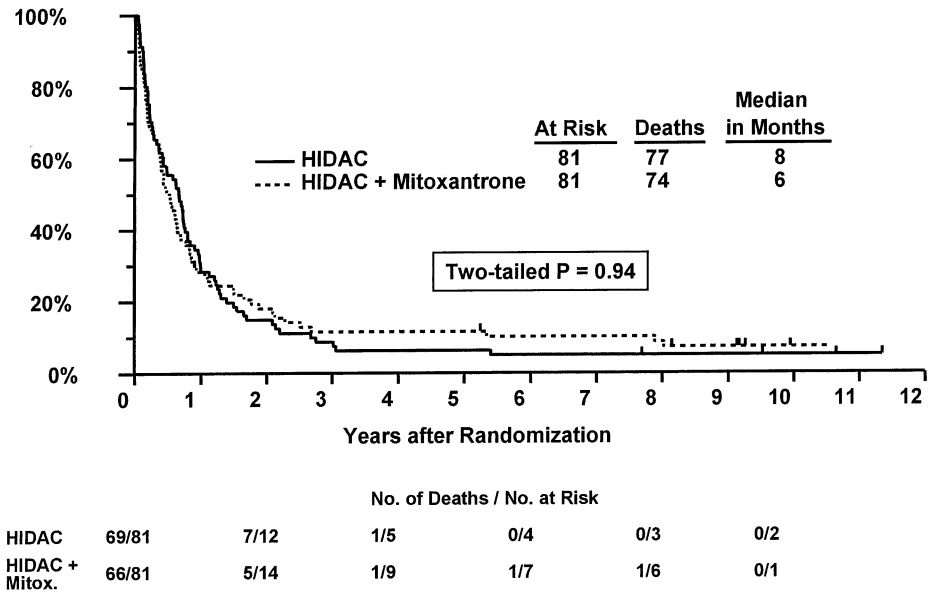

Fig. 2. Overall survival by induction therapy. Kaplan–Meier estimates of the distributions of survival, measured from randomization until death from any cause. Tickmarks indicate censored observations.

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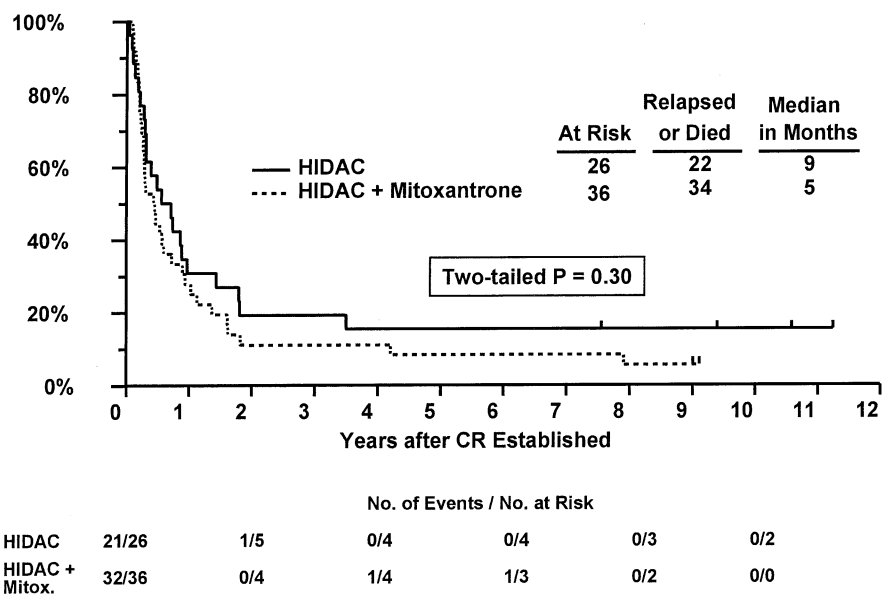

Fig. 3. Relapse-free survival by induction therapy. Kaplan–Meier estimates of the distributions of RFS, measured from an onset of CR until relapse or death from any cause. Tickmarks indicate censored observation.

study design, analysis of the data, drafting of the paper, provided administrative support and gave final approval.

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