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Short communication

Mitoxantrone and cytarabine versus daunorubicin and cytarabine in previously untreated patients with acute myeloid leukemia

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Summary. A total of 44 adults aged 18–78 years were allocated to an open randomized study whose aim was to compare the efficacy and toxicity of mitoxantrone with those of daunorubicin in previously untreated patients presenting with acute myeloid leukemia. In one arm, induction treatment consisted of mitoxantrone plus cytarabine given on a 3- plus 7-day schedule. Post-induction treatment consisted of two courses of mitoxantrone plus cytarabine given on a 2- plus 5-day schedule. In the control arm, mitoxantrone was replaced by daunorubicin. In all, 14 of 21 eligible and evaluable patients in the mitoxantrone arm achieved a complete remission (CR). In the control arm, 14 of 20 subjects attained a CR. The median survival was 365 days for patients randomized to mitoxantrone-cytarabine and 401 days for those given daunorubicin-cytarabine. The efficacy and toxicity of mitoxantrone were similar to those of daunorubicin.

Introduction

The introduction of effective combination chemotherapy in acute myeloid leukemia (AML) has significantly improved remission rates from <30% prior to 1970 to as high as 60%–80% currently [10–12]. The median survival, which was previously only about 2 months from the time of diagnosis, has increased to about 1 year [12]. Unfortunately, the disease relapses in the majority of patients who have entered remission, and a second remission is obtained in only about ≤50% of cases [5, 13, 14]. About 30% of patients survive for 2 years after the initiation of therapy, and a subset of these may be cured of their disease [12]. Clearly, there is a need for more effective therapy at presentation and relapse.

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Standard induction therapy comprises an anthracycline given in combination with cytarabine [4, 9]. The same agents given in combination with other drugs have also been used as consolidation and maintenance therapy for the prolongation of remission duration and survival [8]. Mitoxantrone combined with cytarabine [1, 6, 10] or etoposide [7] has been shown to be effective in the treatment of refractory AML. The administration of anthracycline for a prolonged period is limited by cardiotoxicity. The use in induction treatment of an active agent such as mitoxantrone, which has less potential for cardiotoxicity [2], may improve the overall results.

The objectives of the present study were to compare the efficacy and the acute and chronic toxicity of mitoxantrone with those of daunorubicin (both given in combination with cytarabine) as judged by their ability to induce complete remissions in and to increase the survival of patients presenting with previously untreated AML.

Patients and methods

The present study was designed as a multi-centre, prospective, randomized, open-label study with an active control arm. Criteria for inclusion in the study were a diagnosis of AML based on the FAB classification [3], informed consent to participate, an age of at least 15 years, serum bilirubin levels of <60 mol/l, serum creatinine values of <260 mol/l, and a normal left ventricular ejection fraction. Patients were not eligible if they had received prior chemotherapy or exhibited a history of congestive cardiac failure, unstable angina, cardiomyopathy, or recent myocardial infarction. Patients showing a history of malignant blood disorder were also excluded. There was no upper age limit for participation in the study, but a WHO performance status of 0–3 was required.

Patients were randomized at their entry in the study. In one arm, induction treatment consisted of 12 mg m^{-2} mitoxantrone given intravenously over 15–30 min on days 1–3 plus 100 mg m^{-2} cytarabine given intravenously as a continuous infusion on days 1–7. Post-induction treatment consisted of two courses of 12 mg m^{-2} mitoxantrone given on days 1–2 plus continuous infusions of 100 mg m^{-2} cytarabine given on days 1–5. In the control arm, mitoxantrone was replaced by 45 mg m^{-2} daunorubicin given intravenously over 15–30 min on days 1–3 in the induction course and on days 1–2 in the two post-induction courses.

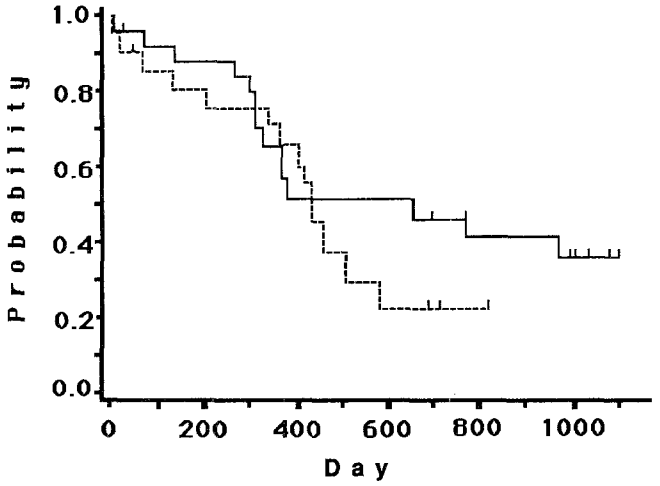

Fig. 1. Life-table plots of survival for 21 patients treated with mitoxantrone-cytarabine (———) and 20 patients treated with daunorubicin-cytarabine (– – –). The difference between the two curves was not significant (log-rank statistic, 1.024; $P = 0.31$). *Vertical marks* denote patients who remain under observation

Patients who achieved a partial remission after induction treatment were treated with a second course containing the initially used drugs, which was given on a 2- plus 5-day schedule. Courses were given at intervals of 4 weeks. No maintenance treatment was used.

Clinical evaluation of anti-leukemic efficacy was based primarily on the percentage of blast cells in the bone marrow and on the bone marrow cellularity. A complete remission (CR) was defined as the attainment of a marrow containing <5% blast cells, a granulocyte count of $>1 \times 10^9$/l, and a platelet count of $>100 \times 10^9$/l. A partial remission (PR) was defined either as the attainment of <5% blast cells in the marrow along with an incomplete recovery of blood counts or as a reduction in the percentage of blast cells in the marrow to 5%–25% along with normalization of blood counts. Failure was defined as the failure to achieve a CR after the completion of one or two courses. During therapy, patients were seen at least once a week for a physical examination, cell counts and biochemical analyses. Urinalysis, electrocardiography, investigations of bone marrow aspirate and evaluations of cardiac function using an isotope method (MUGA) were performed on study entry and after the completion of each course.

All patients who received a single dose of mitoxantrone or daunorubicin were considered to be eligible for evaluation of safety. All subjects who underwent a single course of therapy followed by 2 weeks of observation were regarded as being eligible for evaluation of efficacy. For statistical analysis, Kaplan-Meier plots were used, and survival differences between the two groups were tested by the log-rank test. A value of $P < 0.05$ was considered to be statistically significant.

Results

A total of 44 adults (29 men and 15 women) were entered in the study. The median age of the patients was 52.5 years (range, 18–78 years); 34% of the subjects were >60 years of age. Base-line data, age, sex, performance status, blast-cell percentage, leukocyte count, platelet count, hemoglobin, and FAB type did not differ between the two arms. The doses of cytarabine given to the patients were similar in both arms. There were no differences between the two arms concerning the relationship between the protocol doses of mitoxantrone or daunorubicin and the doses actually given to the subjects. Three patients who were entered in the study were ineligible due to cardiac abnormalities or to a low left ventricular ejection fraction. There were three early deaths: one occurred in the mitoxantrone-cytarabine arm and two were registered in the daunorubicin-cytarabine arm.

In all, 14 (67%) of 21 eligible and evaluable patients in the mitoxantrone arm achieved CRs and 2 attained PRs; there were also 4 failures and 1 early death. In the daunorubicin arm, 14 (70%) of 20 eligible and evaluable patients entered CR; there were also 4 failures and 2 early deaths. Distribution of the response rate by demographic charac-

Table 1. Number of adverse events corresponding to WHO grades 3 and 4 during 120 cycles of treatment with mitoxantrone-cytarabine or daunorubicin-cytarabine

Adverse events	Mitoxantrone-cytarabine[a]		Daunorubicin-cytarabine[b]	
	WHO grade		WHO grade	
	3	4	3	4
Pain/bone pain	2	0	0	0
Bleeding	0	1	0	1
Cardiac:				
Pericarditis	1	0	0	0
Nonspecific toxicity	1	0	0	1
Failure	0	0	0	1
Hypotension	0	0	0	1
Alimentary canal	2	0	8	0
Infection FUO	16	4	14	1
Pulmonary	5	1	0	1
Renal	0	0	0	1
Total number of adverse events	27	6	23	5

[a] 64 cycles
[b] 56 cycles
FUO, Fever of undetermined origin

Table 2. Medi an number of days to recovery of granulocytes and platelets after the start of treatment with mitoxantrone-cytarabine or daunorubicin-cytarabine

Type of therapy	Granulocytes (1×10^9/l)		Platelets (100×10^9/l)	
	Mitoxantrone-cytarabine	Daunorubicin-cytarabine	Mitoxantrone-cytarabine	Daunorubicin-cytarabine
Induction course	30 days	33 days	30 days	26 days
Consolidation 1	30 days	24 days	30 days	24 days
Consolidation 2	50 days	38 days	50 days	38 days

teristics did not disclose any differences between the two arms. Moreover, the response rates were similar in all age groups. The median time to CR was 37 days in the mitoxantrone arm and 49 days in the daunorubicin arm; however, this difference did not reach significance ($P = 0.54$).

The median survival was 365 days for patients randomized to mitoxantrone-cytarabine and 401 days for those given daunorubicin-cytarabine (Fig. 1). The probability of survival seemed to be greater on the mitoxantrone-cytarabine arm at the latter times than on the daunorubicin-cytarabine arm, but the difference between the curves was not statistically significant (log-rank statistic, 1.024 ; $P = 0.31$).

The median duration of CR was 245 days, and there was no significant difference either between the two treatment arms or between the elderly and the younger patients. Only four subjects (two from each treatment arm) proceeded to allogeneic or autologous bone marrow transplantation during their first CR.

No significant difference was found between the two treatment arms in terms of the number and severity of adverse events (Table 1). The cardiac events seen in both arms were not considered to be related to daunorubicin or mitoxantrone treatment, with the exception of one case in the daunorubicin arm in which a possible relationship between daunorubicin and cardiac failure was indicated. Bone marrow toxicity was similar in both treatment arms (Table 2). The recovery of granulocytes and platelets after induction treatment occurred a few days earlier in the mitoxantrone arm than in the daunorubicin arm. However, the situation was reversed following consolidation treatment, when recovery occurred later in the mitoxantrone arm. The median number of platelet transfusions during induction cycle 1 was 4 in the mitoxantrone arm and 3.5 in the daunorubicin arm.

Discussion

The combination of daunorubicin and cytarabine may be regarded as standard treatment for AML. In the present study, patients in one randomization arm were treated with this combination, whereas in the other arm, cytarabine was combined with mitoxantrone. The protocol dose of cytarabine was identical in both arms, and that of mitoxantrone was calculated to produce bone marrow toxicity of the same degree as that resulting from the dose of daunorubicin. Protocol adherence did not differ between the two randomization arms. Patients with poor prognostic features were equally distributed between the two arms.

The efficacy of mitoxantrone given in combination with cytarabine was found to be similar to that of daunorubicin combined with cytarabine, with 67% of patients in the mitoxantrone arm achieving a CR vs, 70% of those in the daunorubicin arm. These figures should be regarded as being acceptable, considering the high median age of the patients (34% of them were >60 years of age). Survival was also found to be similar in both arms, with a median survival of 365 days being achieved on the mitoxantrone arm vs 401 days on the daunorubicin arm. The number of long-term survivors was higher among patients who were treated with mitoxantrone-cytarabine than among those who received daunorubicin-cytarabine, but the difference between the curves was not significant.

The toxicity of mitoxantrone was comparable with that of daunorubicin. Bone marrow toxicity was also similar for both regimens, and there was no significant difference in the time to remission or the time to recovery of granulocytes and platelets. The interesting question as to whether the risk of cardiac toxicity would be lower during mitoxantrone treatment than during daunorubicin treatment could not be answered in this study due to the small number of patients involved, but one case of cardiac toxicity may possibly have been associated with anthracycline therapy in the daunorubicin arm.

In conclusion, considering the size of the population studied, the present results generally agree with recent reports [11]. The efficacy and toxicity of mitoxantrone in the treatment of AML seem to be very similar to those of daunorubicin. If this is confirmed in larger studies, a lower risk for the induction of cardiotoxicity by mitoxantrone as compared with daunorubicin may render mitoxantrone given in combination with cytarabine a first-choice alternative therapy for previously untreated AML.

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