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Mitoxantrone, cytosine-arabinoside and 6-thioguanine (MAT) in the treatment of newly diagnosed acute non-lymphoblastic leukemia in adults

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Between January 1986 and September 1989, 28 patients over the age of 14 years were treated with a combination of mitoxantrone, cytosine-arabinoside (Ara-C) and 6-thioguanine (MAT) at the Kuwait Cancer Control Centre (KCCC). All patients were newly diagnosed cases of acute non-lymphoblastic leukemia (ANLL). Fifty-eight courses of treatment were given as induction and consolidation therapy. The main toxicity was bone marrow suppression. Other toxicities were mainly nausea and vomiting, hepatotoxicity, renal dysfunction and alopecia. In most patients these were mild and tolerable. Complete remission (CR) was achieved in 18 out of 28 (64%) patients. In six patients it was achieved after one course, in 11 patients after two courses and in one patient after three courses. The median survival was 16 months and for those who achieved CR it was 33 months. The actuarial 3 year survival following CR was 43% and the relapse-free survival was 24%. There was little difference in the CR rate for patients below 40 years compared with older patients. However, there was a remarkable difference in survival, with none of the older patients surviving more than 2 years and an actuarial 3 year survival for younger patients of 49%. The study confirms the efficacy of the mitoxantrone-containing combination as a first-line therapy for ANLL.

Key words: Acute non-lymphoblastic leukemia, cytosine-arabinoside, mitoxantrone, thioguanine.

Introduction

During the last few years, many studies have shown the efficacy of mitoxantrone as a single agent[1–5] or in combination with other drugs[6–11] in treating refractory and relapsing acute leukemias. Mitoxantrone is an anthracenedione derivative chemically related to the anthracyclines. It has shown marked anti-tumor activity with fewer toxic effects compared with the anthracyclines, especially with regard to the cardiac toxicity.[12]

Several studies reported using mitoxantrone in combination with other drugs to treat newly diagnosed cases of acute leukemia;[13–15] however, there have been none from the Middle East region. The present paper reports the experience from the Kuwait Cancer Control Center (KCCC) of using mitoxantrone in combination to treat newly diagnosed adult patients with acute non-lymphoblastic leukemia (ANLL). The study reports the pattern of toxicity as well as the efficacy of the combination in controlling the disease.

Patients and methods

Between January 1986 and September 1989, 28 cases of ANLL were treated at the KCCC with a mitoxantrone-containing combination (Table 1). The youngest patient was 15 years old and the oldest 63 years old (Figure 1). There were 15 males and 13 females. The median age was 40 years. All cases were diagnosed by bone marrow examination. The majority of cases were either M2 or M4 ANLL (Table 2). They underwent complete blood count and a biochemical profile every 4 days, and an electrocardiogram (ECG) weekly.

Mitoxantrone was given as an i.v. infusion over 30 min and the cytosine-arabinoside (Ara-C) as a continuous infusion for 5 days. The patients were followed-up till death or for a minimum of 6 months. Only two patients were lost for follow-up after achieving complete remission (CR).

During the period of pancytopenia the patients were nursed in a private room with reverse barrier precautions. After recovery of the peripheral blood and the patient was found in a clinical CR, a bone

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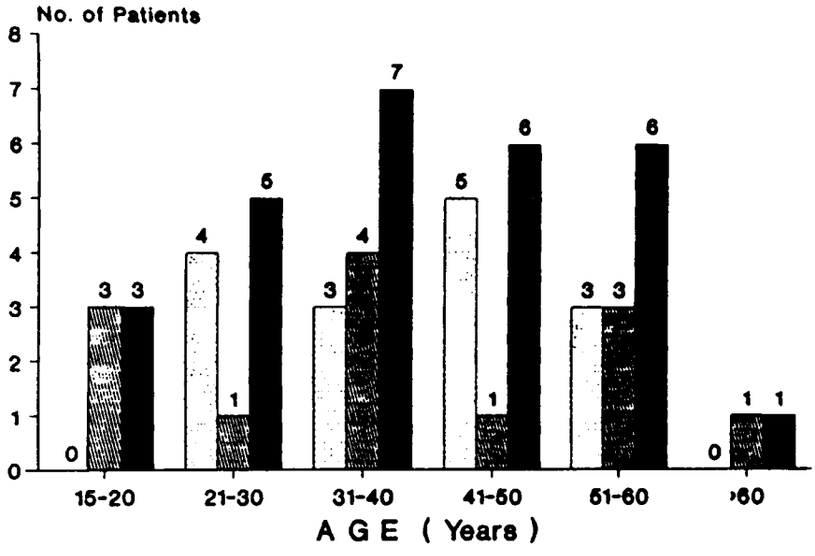

Figure 1. Age and sex distribution: ▨, males; ▩, females; ■, total.

Table 1. MAT combination

Mitoxantrone	10 mg/m^2/day i.v. days 1–3
Ara-C	100 mg/m^2/day i.v. infusion days 1–5
6-Thioguanine	100 mg/m^2/day p.o. days 1–5

Table 2. Types of ANLL

Type	No. of patients
M1	4
M2	8
M3	2
M4	11
M5	2
M6	1
Total	28

Table 3. Courses to CR

No. of courses	No. of patients
1	6
2	11
3	1
Total	18

marrow examination was performed. If CR was not confirmed (blasts >5%), another course was given. Consolidation courses were given to eight patients. They ranged between one and two courses. They were mostly those who achieved CR after one course.

Analysis included all patients, even those who were in very poor condition prior to therapy and who died shortly after initiation of treatment.

Patients included in the study were informed about the aims and targets of the study as well as of any potential side effects from their participation. Only consenting patients were included in the study.

Results

Four patients died shortly after starting therapy: six patients received more than one course of therapy and achieved only a short-lived partial remission; 18 patients (64%) achieved CR, mostly after two courses of therapy (Table 3). The median survival for all patients was 16 months. Those who achieved CR had a median survival of 33 months and a median relapse-free survival of 23 months. The actuarial 3 year survival following CR was 43% and the relapse-free survival was 24%. Those who did not achieve CR died within 1 year (Figure 2).

Patients below 40 years of age did better than older patients. The CR rate was 69% versus 60%, respectively. The 3 year actuarial survival for those

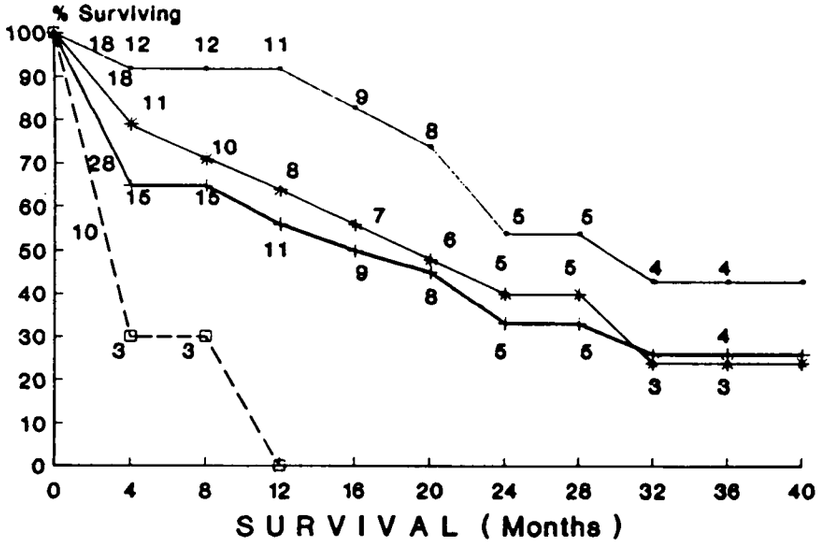

Figure 2. Overall survival and relapse-free survival: +, overall survival; ●, overall survival after CR; *, relapse-free survival after CR; □, overall survival after partial response or no response.

below 40 was 49%, while none of those above 40 survived more than 2 years (Figure 3).

Toxicity

The 28 patients received 58 courses as induction and consolidation therapy. The toxicity was assessed in relation to each course (Table 4).

Nausea and vomiting. Most patients who suffered from this toxicity had only nausea. Vomiting occurred after seven courses (12%) and was severe after only three courses.

Stomatitis. The median time to its appearance was 8 days from the start of the course. It usually lasted for 7–10 days. After only one course it was severe

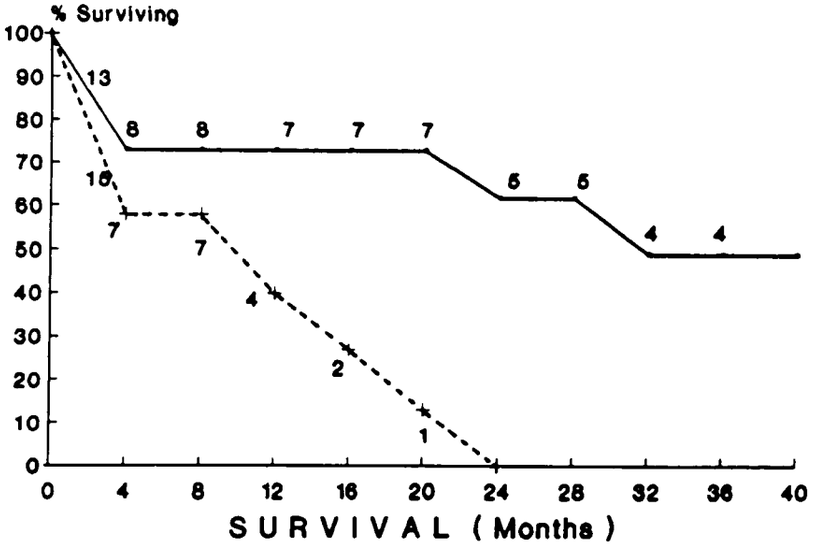

Figure 3. Overall survival and age: —, 15–39 years; ----, >39 years.

Table 4. Toxicity after 58 courses of therapy

Toxicity	No. of courses	(%)
Nausea and vomiting		
mild and moderate	25/58	43
severe	3/58	5
Stomatitis		
mild and moderate	20/58	34
severe	1/58	2
Hepatotoxicity	14/58	24
Renal toxicity	15/58	26
Pancytopenia	58/58	100
Alopecia[a]		
partial	13/28	46
total	8/28	29

[a] Related to number of patients.

enough to necessitate parentral nutrition for a few days.

Hepatotoxicity. Disturbances in the liver function were observed following 14 courses. An isolated rise in alkaline phosphatase level occurred after six courses. In the remainder, the rise in alkaline phosphatase was accompanied by a rise in transaminases. The bilirubin level increased significantly only following one course. The hepatotoxicity started to show on day 10 from the start of the course, lasted for an average of 12 days and then started to improve slowly. Some patients received another course of therapy before full recovery of the hepatic disfunction. Further deterioration was not observed in these patients. The recovery process continued.

Renal toxicity. Renal toxicity represented a transient rise in the serum creatinine level. It ranged between 30 and 100% of the pre-therapy level. Mostly it was observed on day 4 and reverted to pre-therapy levels on day 12.

Alopecia. Seven patients (25%) had no appreciable hair loss following therapy. Those who had partial alopecia had acceptable hair and did not need any wigs.

Bone marrow toxicity. All courses were followed by a period of severe pancytopenia after a median time of 8 days. Thrombocytopenia usually recovered by day 18 and neutropenia followed in 2–3 days.

Other toxicities. Three courses were followed by severe diarrhea necessitating intensive supportive therapy. During the period of neutropenia three patients developed abscesses. Two in the perianal region and one in the face. Another patient developed pulmonary and systemic aspergillosis and died.

Discussion

Several studies from the US and Europe explored the efficacy of mitoxantrone in combination with other drugs in the treatment of newly diagnosed cases of ANLL. In a phase II pilot study[15] remission induction using mitoxantrone and Ara-C yielded a CR rate of 79% in 29 newly diagnosed patients with ANLL. In a Latin American clinical trial[14] comparing mitoxantrone and Ara-C versus daunorubicin and Ara-C, CR rates of 50 and 40%, respectively, were observed. There was no significant difference in the time to CR or the median relapse-free survival in the 102 patients analyzed. In a large multicenter US study in newly diagnosed ANLL patients, mitoxantrone (12 mg/m^2/day for 3 days) plus Ara-C (100 mg/m^2/day for 7 days) achieved a CR rate of 63% compared with 53% achieved with daunorubicin plus Ara-C.[6] In the same study, more patients in the mitoxantrone group achieved CR after one induction course (63 versus 56%).

The present phase II pilot study used a lower dose of mitoxantrone (10 mg/m^2/day) compared to that used in the above studies (12 mg/m^2/day); however, in our study 6-thioguanine was added to the combination. Apart from hematopoietic toxicity, all other toxicities were mainly of a mild degree and were very well tolerated. We did not observe any serious cardiac toxicity. The hepatic toxicity was transient, although usually slow to recover.

We observed very mild and transient renal toxicity, as was reported previously in a study.[11] This may require special care if the combination is used to treat patients with poor renal function. One quarter of our patients did not suffer any appreciable degree of alopecia. Nearly half the patients suffered only partial alopecia of an acceptable degree.

These lower toxic effects are an improvement over the daunorubicin-containing combinations where nausea and vomiting are more frequent and more intense, and the alopecia almost always total. In our study the CR rate was 64%. In most cases it was achieved after two courses of treatment. This may be due to the lower dose of mitoxantrone used.

There was a marked difference in survival in favor of those below 40 years of age, despite the little difference in CR rates. This may be due to a less favorable response for second-line therapies following relapse in older patients.

Conclusion

The results of this study support the use of mitoxantrone in combinations as a first-line therapy in ANLL. This proved effective and tolerable in a hospital setting lacking sophisticated isolation measures (laminar flow rooms) and strict sterilization facilities.

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