

## ADULT ACUTE MYELOBLASTIC LEUKEMIA: EXPERIENCE AT KING KHALID UNIVERSITY HOSPITAL

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**Background:** The clinical features of acute myeloblastic leukemia (AML) and its response to therapy in adult patients in Saudi Arabia are not well defined, as only scanty data has been available. This situation will likely continue unless experience with AML is reported from different institutions in the Kingdom.

**Patients and Methods:** In this retrospective study, the records of 52 adult patients with previously untreated *de novo* acute myeloblastic leukemia (AML) who were treated at King Khalid University Hospital over a five-year period from January 1989 to December 1993 according to the conventional "3+7" regimen were reviewed. The clinical features of the disease, response to therapy and treatment-related complications were identified.

**Results:** There were 33 males and 19 females with a mean age of  $30 \pm 13$  years (mean  $\pm$  SD). M4 and M5 AML were the predominant French-American-British (FAB) subtypes encountered. Sixty-five percent of patients achieved complete remission (CR). The median duration of the first CR of all analyzable patients was 32 weeks. The median CR duration and survival of patients achieving complete remission who survived through their consolidation treatment was 36 and 49 weeks, respectively.

**Conclusion:** Both median duration of the first complete remission and survival compare unfavorably with those reported in the literature despite a comparable remission rate. Infectious complications were frequent and accounted for a significant number of mortalities.

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**Key words:** Leukemia, myeloblastic, AML, chemotherapy.

Acute myeloblastic or non-lymphoblastic leukemia (AML or ANLL) is a well-characterized, highly lethal human neoplasm that is potentially curable. With the introduction of improved supportive care and effective cytotoxic agents, complete remission (CR) rates of 50%-70% have been reported in the literature.<sup>1,2</sup> Like many other diseases described in the literature, AML characterization usually originates from the experience accumulating in the Western world. Whether such disease characterization holds true when applied to patients in the developing countries is uncertain.

Scanty data has been published about AML in the Kingdom of Saudi Arabia. The clinical features of the disease and patients' response to therapy remain poorly defined. This situation will continue until adequate data becomes available. In this report, we describe our single institution experience with AML patients seen over a five-

year period. To the best of our knowledge, this series constitutes the largest clinical report to be published about AML in adult patients treated in the Kingdom.

### Patients and Methods

This is a retrospective study of all adult patients admitted to King Khalid University Hospital (KKUH) and diagnosed to have previously untreated *de novo* AML over a five-year period extending from January 1989 to December 1993. The diagnosis of AML was established according to the standard practice, and based at least on peripheral blood and bone marrow morphology and cytochemistry. Immunophenotyping and cytogenetic analysis were carried out for most patients. Patients with blast crisis of chronic myelogenous leukemia and those thought to have secondary AML were excluded from the study. Patients who had received any prior cytotoxic therapy and those who had been treated for their leukemia with any regimen other than the study regimen outlined below were also excluded.

### Treatment Regimen

Only patients who received remission induction chemotherapy according to the standard 3+7 regimen

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(consisting of three days of daunorubicin at a daily dose of 50 mg/m<sup>2</sup> and seven days of cytosine arabinoside at a daily dose of 200 mg/m<sup>2</sup> administered by continuous intravenous infusion) were included in the study. All patients achieving CR were given identical regimens for consolidation. Patients who failed their initial induction were reinduced by a second cycle of the same regimen. All patients had had Hickman indwelling central venous catheters either before, or soon after the initiation of cytotoxic therapy. A single dose of vancomycin was given to all patients prior to catheter insertion.

#### *Patient Monitoring*

Complete and differential blood counts were performed daily on all patients from the day the diagnosis was established until full hematological recovery or discharge from the hospital. All patients had a full baseline biochemical profile, daily serum electrolytes, urea and creatinine, liver profile, serum magnesium and calcium levels, as well as coagulation profiles at least three times per week. Bone marrow examination was performed in all patients to establish the initial diagnosis and at least once thereafter, to establish the response to therapy and remission status. Bone marrow examination was to be repeated once weekly if hematological recovery did not take place by the 28th day of treatment and until a conclusive response status was defined.

#### *Supportive Care*

Transfusion of blood components was based on pre-written conditional orders according to the result of the daily blood counts. Two units of leukocyte-depleted packed red blood cell concentrates were transfused for hemoglobin values less than 90 g/L. Six units of leukocyte-depleted random donor platelets or one single donor platelet collection were infused for platelet counts of less than 20 x10<sup>9</sup>/L on daily blood counts. Invasive procedures and bleeding episodes were covered with additional platelet transfusions according to individual needs.

Empirical broad-spectrum antibiotic coverage was initiated following a full septic work-up in all patients who showed a single episode of oral temperature rise >38 °C, or three consecutive episodes of temperature rise to 38 °C within a period of 24 hours unrelated to the transfusion of blood components. Our initial antibiotic regimen consisted of a combination of ceftazidime and amikacin in appropriate dosing, given every 8 or 12 hours, respectively. Unless included in the initial antibiotic regimen, vancomycin was added only if fever persisted for 48 hours and the blood culture results were still not conclusive. Empirical antifungal coverage with amphotericin B was added if the patient remained febrile for an additional 48 hours after the inclusion of vancomycin. Antimicrobial coverage was optimized according to the microbiological culture results.

#### *Response Criteria*

Complete remission (CR) was defined as the presence of <5% blast cells in a normocellular bone marrow with at least low normal peripheral blood counts and the disappearance of all clinical evidence of the disease. Partial remission (PR) required similar criteria but was associated with more than 5% blast cells in the bone marrow. Patients failing the induction therapy were categorized as 1) early deaths, if they died within the first two weeks of therapy; 2) death during neutropenia, if they died after the first two weeks of therapy but before recovering absolute neutrophilic count of >0.5 x 10<sup>9</sup>/L; or 3) refractory to initial therapy if they failed to achieve a CR by the completion of two cycles of the induction regimen. Alternative therapy would have been considered for patients categorized to have refractory disease.

### **Results**

A total of 59 adult patients with previously untreated *de novo* AML fulfilling the study inclusion criteria were identified. Seven patients were excluded from the study because of incomplete records. The study population consisted of 52 patients with a mean age of 31.4±13.7 years (mean±SD). There were 33 males and 19 females. There were 35 Saudi patients (21 males and 14 females) and 17 non-Saudi patients (12 males and 5 females). The clinical features at presentation are outlined in Table 1. Tables 2 and 3 describe the frequency of AML subtypes according to the French-American-British (FAB) classification and the outcome of therapy, respectively.

#### *Toxicity and Deaths*

There were 17 deaths in the study population: four early and six neutropenic deaths during induction therapy and seven neutropenic deaths during consolidation therapy. Of the 10 deaths which occurred during induction therapy, eight were attributed to sepsis, one to cerebral hemorrhage, and one to pulmonary hemorrhage. All seven deaths which occurred during consolidation treatment were attributed to sepsis. Grade IV hematological toxicity occurred in all patients. Grade II-III toxicity affecting the gastrointestinal tract occurred in 34 patients (65%). Grade II-III alopecia was virtually observed in all patients. Grade I nephrotoxicity was seen in 15 patients (29%), and was mainly attributed to the use of nephrotoxic antimicrobial agents.

#### *Infectious Complications*

During a total of 98 courses of induction, reinduction and consolidation treatment, there were 31 bacterial isolates. Twenty-three isolates were associated with septicemia (positive blood cultures), while the remaining eight isolates were cultured from non-hematogenous body sites. Gram-negative organisms accounted for 67% of

TABLE 1. Clinical features at presentation in 52 adult patients with acute myeloblastic leukemia (AML).

Clinical features	No. of patients	Percentage
Pallor	36	69
Fever	18	34.6
Petechial bleeding	16	30.7
Splenomegaly	16	30.7
Gum hypertrophy	12	23
Lymphadenopathy	11	21
Sternal tenderness	9	17.3
Hepatomegaly	7	13.5
Fundal hemorrhage	6	11.5
Conjunctival hemorrhage	5	9.6
Lung infiltrate	4	7.6
Rash	4	7.6
Jaundice	4	7.6
CNS disease, pregnancy, clubbing, chloroma	1 each	2% each

septicemic cases and all the other non-septicemic bacterial infections. Gram-positive organisms accounted for 33% of septicemic cases and none of the other infections. There were six episodes of fungemia and five episodes of fungal infection without fungemia. Dual infection septicemia was documented on three occasions, single organism septicemia and fungemia was documented on one occasion. Non-septicemic dual bacterial infection occurred in one patient, while non-septicemic single bacterial infection and single fungal infection without fungemia occurred in another patient. *E. coli* was the most frequent gram-negative isolate from blood cultures, while *Staphylococcus epidermidis* was the most frequent gram-positive septicemic isolate. *Klebsiella* species was the most frequent organism responsible for non-septicemic infections. *Candida albicans* was the most common fungal isolate. *Mycobacterium tuberculosis* was detected in the Ziehl-Neelsen smear of a lymph node biopsy in a leukemic patient who presented with mediastinal lymphadenopathy and clubbing of the fingernails, and was cultured from the pleural fluid of another leukemic patient who had unexplained pleural effusion at presentation.

#### CR Duration and Survival Data

Data on median duration of first CR was available on 30 of the 34 patients who achieved CR following one or two courses of induction chemotherapy and who went on to receive consolidation chemotherapy. The median first CR duration for these 30 patients was 32 weeks (range 8-72 weeks). As seven of these patients died during consolidation chemotherapy, the median first CR duration for the remaining 23 patients was 36 weeks (range 16-72 weeks). Survival data was available on 21 of these 23

patients only. The median survival for those 21 patients was 49 weeks (range 16-94 weeks).

#### Discussion

The frequency of different FAB subtypes of AML varies, depending on the study. Most published data indicate the predominance of M 1 and M 2 subtypes.<sup>3-7</sup> M 1 and M 2 AML were described to account for 7%-30% and 14%-63% of all cases of AML reported in these large series, respectively. In contrast to this reported frequency, our series confirms the predominance of M 4 and M 5 subtypes, which has been previously observed in the Kingdom. A frequency rate of 57% and 13% for M 4 and M 5, respectively, was reported in AML patients older than 12 years of age.<sup>8</sup> Roberts and associates reported a frequency rate of 39% for M 4 and 18% for M 5 AML in Saudi patients older than 15 years of age.<sup>9</sup>

The mean patient's age at presentation in our series seems to be lower than the expected mean age reported in the Western countries, where AML peaks in incidence after the sixth decade of life.<sup>10</sup> This apparent discrepancy could be explained at least in part by the referral bias and pre-admission selection of patients, which is not unusual for any tertiary care center, especially in cases of limited resources.

Little has been published about the pattern of clinical presentation for AML patients in Saudi Arabia. Our data does not indicate significant differences in the presenting features of the disease, with the possible exception of the presence of splenomegaly, which was detected in about one-third of our patients. Splenomegaly has been reported to be present in 10% of patients at presentation.<sup>11</sup>

The treatment of AML consists primarily of remission induction and post-remission or consolidation therapies. The combination of cytosine arabinoside with an anthracycline antibiotic is considered conventional. The most commonly used regimen is the so-called 3+7 regimen.<sup>1,2,12</sup> With such a regimen a CR rate of 53%-72% and median remission duration of 10-18 months have been described.<sup>1,2,12-15</sup> Our CR rate was 65% and compares favorably with that reported in the literature. The median duration of the first CR and the median survival in our patients of 32 and 28 weeks, respectively, were inferior to the published data. This inferior result can be partially accounted for by the septic death of seven patients during the consolidation phase of the treatment. The median duration of first CR in the 23 patients who survived their consolidation treatment was 36 weeks, while the median survival of patients who achieved CR and survived through the consolidation phase and in whom survival data was available was 49 weeks. These data clearly indicate a significantly shorter CR duration in our patients. A possible explanation for these unfavorable results is that a large proportion of our patients had M 4 and M 5 AML. Both these types of leukemia are believed to behave

TABLE 2. French-American-British (FAB) subtypes in 52 adult patients with AML.

FAB subtype	No. of patients	Percentage
M 0	0	0
M 1	1	2
M 2	2	4
M 3	9	17
M 4	21	40
M 5	17	33
M 6	0	0
M 7	2	4

TABLE 3. Treatment outcome in 52 adult patients with AML.

Outcome	No. of patients	Percentage
CR rate	34	65.3
After one induction	22	42.3
After two inductions	12	23
PR rate	3	5.8
Refractory disease	3	5.8
Early death	4	7.7
Neutropenic death	6	11.5
Unknown outcome	2	3.8

differently from the remaining AML subtypes. Patients with the monocytic leukemias are reported to have decreased CR rates, early relapses, failure to achieve a second CR and decreased survival.<sup>16-18</sup> Despite all the progress that has been achieved in leukemia management and the advances in the supportive care of patients undergoing treatment, infection remains a major cause of morbidity and mortality in leukemic patients. The relatively high rate of septic complications in our patients is the major factor accounting for the high percentage of treatment-related deaths. The pattern of the infectious complications we encountered was essentially similar to that previously reported from our center.<sup>19</sup> There was, however, a lesser percentage of isolates in this series. Similar to the previous study, a high frequency of fungal infections occurring in 10% of all patients was encountered. This rate of fungal infection clearly outnumbers the rate reported in some Western studies.<sup>20</sup> Tuberculosis was diagnosed in one patient at presentation and confirmed later in another patient in this series. Concurrent cases of acute leukemia and tuberculosis are well recognized in the literature.<sup>21,22</sup> A recent report from the M.D. Anderson Cancer Center estimated the frequency of tuberculosis in cancer patients to be 90 per 100,000, being most common in leukemics.<sup>23</sup> A higher frequency rate would naturally be expected in countries where the disease is endemic. Our limited experience with these two patients suggests that, in highly endemic areas for

tuberculosis, the disease will have to be considered as a possible cause of persistent fever in neutropenic patients on maximal antimicrobial coverage, especially when pulmonary infiltrate or unexplained pleural effusion are detected. Decisions for the empirical initiation of antituberculous treatment have to be individualized depending on the clinical circumstances and the condition of the patient.

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