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Long-term outcomes of Acute Myeloid Leukemia in Adults in Pakistan

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Abstract

Objective: To describe the long-term outcomes of Acute Myeloid Leukemia (AML) and to study clinicopathological features at presentation, morphological subtypesand remission rates.

Methods: Demographic information, response to therapy and survival of patients (>14 years of age) admitted between January 1988 to August 1996 with acute myeloid leukaemia was retrieved and analysed.

Results: Seventy-four patients were admitted with a diagnosis of AML during the study period. There were 43 males and 31 females. Age ranged between 15 and 70 years with a mean age of 38 years. The most common presenting feature was fever (67.5%) and the morphological subtype according to French-American-British Group (FAB) criteria was M4. Fifty-five patients received treatment and were evaluable for response and outcomes. Thirty-six (65.4%) patients had complete remission. Sixteen (29.1%) died during the first 28 days after starting induction chemotherapy. The median survival was 11 months. Six (11%) patients (4 females, 2 males) are surviving beyond 4 years (long-term survivors).

Conclusion: Our study suggests that the long-term outcomes of adults with AML are comparable to what has been reported in the literature for patients who do not receive bone marrow transplants (JPMA 52:482;2002).

Introduction

Acute myeloid leukemia (AML) constitutes 12% of acute leukemias under the age of 10 years, 28% between ages 10-15 years and 80-90% of cases in adults[1]. Whereas the mean age at presentation is 55 years, the incidence increases with age[2]. A remission rate of 50-70% has been observed with the current chemotherapeutic regimens and supportive care[3], However, the vast majority of patients relapse and only 10-15% live for five years or more after the diagnosis[4-6]. These figures are derived from studies conducted in North America and Western Europe and may not reflect the pattern of disease in the developing world. It is known that there are some important differences amongst patients due to ethnic, socioeconomic and environmental factors[7]. The Aga Khan University Hospital is a tertiary referral and a specialist haematology center. Patients are referred from all over the country, the majority being from the regional areas. In this report, we present the clinicopathological features, remission rates and long-term outcomes of AML in adults in Pakistan.

Patients and Methods

The data were collected retrospectively and covered a study period between January 1988 and August 1996. Consecutive patients diagnosed to have AML and admitted to the hospital were enrolled. The medical records of all the patients above the age of 14 years were retrieved. The diagnosis was logged on the face sheet by the admitting Physician. The medical records department uses International Classification of Diseases (lCD) version 9.0. The patients were followed up till the end of December 2001 and hence a minimum of 40 months of follow up was available on all the patients. The

chemotherapy regimens are as under: Induction chemotherapy with Cytosine arabinoside (Pharmacia-Upjohn, Stockholm, Sweden) 100 rng/m^2 continuous intravenous infusion for 7 days and either Daunorubicin (Pharmacia-Upjohn, Stockholm, Sweden) 45 mg/rn^2 intravenous bolus for 3 days or Mitoxantrone (Lederle, Baulkham Hills, Australia) 12 mg/m^2 intravenous bolus for 3 days. Etoposide (Bristol Myers-Squibb SpA, Latina, Italy) 100 mg/m^2 was administered as intravenous infusion over 2 hours for 4 days in addition to the induction regimens for patients with M4 or MS FAB (French-American-British classification) subtypes[8]. Remission status was checked on the 10th day and after 3 weeks of induction chemotherapy. Six patients with M3 FAB subtype received All-trans retinoic acid (ATRA) (Hoffman-La Roche, Paris, France) at dose of 45 mg/m^2 either alone (n=3) or in conjunction with chemotherapy (n3)[9] for induction of remission. Once patients were in remission, two courses of consolidation chemotherapy were given, consisting of cytosine arabinoside 100 mg/m^2 for 5 days and either Daunorubicin 45 mg/m2 for 2 days or Mitoxantrone 12 mg/m^2 for 2 days. High-dose Cytosine arabinoside at a dose of 3.0gm! m^2 per day in two divided doses for 3 days was administered for consolidation of remission[10]. A total of 3 courses were given at an interval of 3-4 weeks. The data are expressed as meanES.D. and as percentages where appropriate. Kaplan and Meier curves were used for survival analysis[11].

Results

Between January 1988 and August 1996, a total of 74 patients above the age of 14 years were admitted to the hospital with an underlying diagnosis of AML. There were 43 males and 31 females with a male to female ratio ofcommonest presenting symptom was fever (67.5%), followed by the symptoms of anaemia (45.9%) and bleeding (29.7%). Other significant presenting features included admission at our hospital and were admitted with a septic episode while two had intra-cerebral bleed. A total of 55 patients received chemotherapy and were evaluable for response and toxicity. Thirty-six out of 55 (65.4%) patients entered complete remission (CR). Sixteen (29.1%) died during the first 28 days after starting induction chemotherapy (early mortality). The median survival was 11 months. The overall survival of these patients is shown in Figure. Two patients received allogenic bone marrow transplantation in the UK, however, their overall survival was 6 and 12 months only.1.3:1.0. Their ages ranged between 15 and 70 years. The mean age at the time of diagnosis was 38 years. The anorexia, weight loss, fatigue and headaches. One patient was diagnosed incidentally.
Overall 55 (74.3%) had fever. Only 30 (40%) had a microbiological focus and 17 (22%) patients had a clinical source of infection. The commonest morphological subtype according to the FAB criteria8 was M4, details are shown in Table 1.

Table 1. FAB subtypes and comparison with other studies.

FAB Type	Sultan et al (1980) n=250 %	Mertels-mann et al. (1980) n=263 %	ECOG (1981) n=300 %	van der Reijden (1983) n=55 %	Hassan et al. (1993) n=62 %	Chaudhry et al. (1993) n=54 %	Present study (2002) n=74 %
M0	-	-	-	-	1.61	-	-
M1	21	9.6	10	16.3	22.58	13	8.1
M2	32	29.4	30	29	32.26	44.4	16
M3	16	15.8	11	5.4	9.68	11.1	15
M4	16	8.5	37	7.2	22.58	24	46
M5	12	33.6	9	36.7	8.06	3.7	9.5
M6	3	3.1	3	5.4	1.61	3.7	0
M7	-	-	-	-	1.61	-	2.7

The haematological and biochemical features are shown in Table 2.

Table 2. Laboratory features at presentation.

	Mean	Range
Haemoglobin (gm/dl)	8.3±2.4	3.6-13.2
Total leukocyte count (x10^9/L)	49.7±62.4	0.4-256
Platelets (x10^9/L)	65.2±60.2	1-192
Serum creatinine (mg/dl)	1.2±1.14	0.6-6.1
Total bilirubin (mg/dl)	1.28±1.30	0.2-7.3
Alanine aminotransferase (IU/L)	27±29.7	10-192
Lactate dehydrognase (IU/L)	1520±1733	45-8137
Uric acid (mg/dl)	5.04±3.6	1.6-16.6

The mean haemoglobin concentration was 8.3 gm!dl, mean leukocyte count was 49.7x109/L and the mean platelet count was 65.5x109/L. Fifty-three (71.5%) patients had haemoglobin (Hb) <10 gm/dl while 13 (18.9%) presented with a total leukocyte count (TLC) >100 x 109/L (hyperleukocytosis). Mean lactate dehydrogenase (LDH) level was 1520 IU/L.

Ten (13.5%) patients did not receive treatment and left hospital after the diagnosis because of several reasons including financial constraints. Nine (12.2%) patients died before the treatment could be commenced at our hospital. Seven of these patients presented with signs of sepsis. Out of these 9 patients, 5 had pneumonia, and two had received chemotherapy prior to admission at our hospital and were admitted with a septic episode while two had intra-cerebral bleed. A total of 55 patients received chemotherapy and were evaluable for response and toxicity. Thirty-six out of 55 (65.4%) patients entered complete remission (CR). Sixteen (29.1%) died during the first 28 days after starting induction chemotherapy (early mortality). The median survival was 11 months. The overall survival of these patients is shown in Figure. Two patients received allogenic bone marrow transplantation in the UK, however, their overall survival was 6 and 12 months only.

Six (fl%) patients are surviving beyond 4 years (long-term survivors). Of these 4 are female and 2 males. One patient developed non-Hodgkins lymphoma (NHL) 3 years after diagnosis. He went into complete remission after receiving chemotherapy for NHL for two years. He remains alive with CNS disease. One patient had M2 FAB subtype, 2 had M3, 2 M4 and one M5 subtype. Only one patient presented with hyperleukocytosis. The same patient had trisomy 8 on karyotyping. Age, gender, FAB subtype, presenting Hb. TLC, platelets, LDH, bilirubin and creatinine were tested and found not significant on univariate analysis for long-term survival. The features of long-term survivors are shown in Table 3.

Table 3. Features of long-term survivors.

No.	Age[1]	Sex[2]	Diagnosis[3]	FAB[4]	WBC[5]	LDH[6]	Chromosomes	Survival[7]
1.	17	M	Nov. 1993	M3	6.0	822	ND	91
2.	22	M	Feb. 1995	M4	7.0	791	ND	76
3.	55	F	May 1995	M2	2.7	679	ND	73
4.	17	F	July 1996	M3	1.8	722	ND	59
5.	15	F	Sept. 1996	M5	112	1166	Trisomy 8	60
6.	17	F	Dec. 1996	M4	4.0	1353	ND	54

1 = Age in years, 2= M = Male, F = Female, 3 =Date of diagnosis, 4 = French American British classification, 5 = White cell count at presentation X 109/ L, 6 =Lactate dehydrogenase mg/ dl, 7 = overall survival in months. ND = Not done

Discussion

There is very little information available from developing Asian countries including Pakistan about the outcome of AML treatment. We undertook this study to examine the features of long-term survivors after treatment for AML. Several clinical and laboratory features at presentation were studied to see whether these predict for long-term survival.

FAB Cooperative Group classification is now universally accepted as the basic morphologic criteria to study different aspects of acute leukaemia[8]. In our study, M4 was the most predominant FAB subtype (46%), followed by M2 (16%), M3 (15%) and MS (9.5%). Our findings are consistent with the Eastern Cooperative Oncology Group experience[12]. However, they are at variance with some other (Table 1). In all these studies the predominant subtype was M2. M5 was noted to be the commonest subtype in the studies of Mertelsmann et al[14] and van der Reijden et al[15]. It is shown that AML FAB M4 is common in Australian population compared to Japanese, where FAB M2 is a common AML subtype[18] suggesting a possible genetic susceptibility to a particular subtype of acute myeloid leukaemia. It is thus likely that certain genetic factors as MLL gene rearrangement play a role in causing a particular FAB subtype of AML in our population. For example, MLL (ALL-i) gene has been associated with AML FAB subtype M4 in Italian population particularly in young adults and children[19].

The mean age at presentation is also at variance with several studies where the mean age at presentation of patients with AML is described as 50 years with incidence increasing with age[20]. Environmental factors such as viruses and pollutants in the food chain or genetic factors possibly play a role in causing AML at a younger age in our patients.[21,22]

The clinicopathological features in our patients reveal that the disease was observed to be at an advanced stage at the time of presentation. In our patients the mean value of Hb. was 8.3 gm/dl which is lower than the mean value of Hb. reported by Sultan et al[13]. Similarly the mean platelet count (65.2 X 10^9/L) was also lower as compared to the mean platelet count (82 X 10^9/L) reported by same authors[13].

Fever (67.5%) and infection (39% clinical and 22% microbiological) were found to be greater as compared to those reported by Keating et al[23] where fever (34%) and infection (clinical 16% and microbiological 22%) were not the major presenting features. This could be because of late presentation of patients at our hospital, which is a tertiary care center. The remission rate of 65% is comparable with the Eastern Cooperative Oncology Group experience of 57%[24], North American

Marrow transplant group reported a disease-free survival of 49% and University of Minnesota Masonic cancer centre reported disease-free survival of 28%[25] in the patients treated with chemotherapy alone. The better long-term disease-free survival figures in these studies are probably due to use of high-dose cytosine arabinoside along with daunorubicin after the patient entered remission. We on the other hand used high-dose cytosine arabinoside alone in most of our patients once they entered remission. On the contrary M.D. Anderson cancer centre group reports a long-term remission rate of l0.7%[26]. Southwest oncology group reported a long-term disease-free survival of 21% when they used high-dose cytosine arabinoside for induction and during consolidation therapy[27]. They further report that when standard-dose cytosine arabinoside was used for induction and high-dose cytosine arabinoside for consolidation the long-term disease-free survival rate fell to 11%. They also reported that in the cohort of patients in which standard-dose cytosine arabinoside was used for both induction and consolidation therapy the long-term disease-free survival was only 6%. The better survival in the group of patients receiving high-dose cytosine arabinoside for induction and consolidation was at a cost of greater toxicity and mortality. In the group of patients receiving high-dose cytosine arabinoside the toxicity rate was 14% compared to 5% in the group which received standard-dose cytosine arabinoside[28]. In this study we reported the long-term disease-free survival of 11% and we too used standard-dose cytosine arabinoside for induction and high-dose cytosine arabinoside for consolidation therapy. The Memorial Sloan-Kettering cancer centre and Southeastern cancer study group reports a long-term disease-free survival of 15% in the group of patients treated with idarubicin and cytosine arabinoside and 7% in the group of patients treated with daunorubicin and cytarabine as induction chemotherapy[29]. We however, found a long-term survival of 11 % when we used daunorubicin and cytosine arabinoside as induction chemotherapy. Bennett et al. reported a long-term survival of 19.3% when they used standard-dose cytosine arabinoside and daunorubicin[30].

Six (11%) of our patients are surviving equal to or beyond 4 years without disease. Our results of long-term disease-free survival are comparable to most published studies on this subject. We however, report a high early mortality rate of 29% and this is probably due to late presentation. Majority of our patients had sepsis at the time of presentation and as many as 30 (54.5%) had high leukocyte count of greater than 20×10^9/L and 43 (78.1%) had haemoglobin lower than 10 gm/dl. It is reported that female gender, leukocyte count less than 10×10^9/L and haemoglobin greater than 10 gm/dl are associated with longer disease-free survival[30].

Univariate analysis of various factors failed to predict long-term survival in our group of patients. A level of statistical significance may have been achieved due to either a small sample size or to a different nature of the disease.

In conclusion our data shows that long-term survival of adults with AML when treated with chemotherapy alone is comparable to what has been reported in the literature, We did not find any factor that may predict long-term survival in these patients.

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