

Cost and Outcome of Treatment of Adults with Acute Myeloid Leukemia at the National Cancer Institute-Egypt

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ABSTRACT

Background: Despite important advances in the therapy of acute myeloid leukemia (AML), the majority of patients die of their disease, unless bone marrow transplantation (BMT) is done. Infection and hemorrhage are still the major causes of mortality in AML patients. Progress in therapy and supportive care has led to gradual improvement in the overall results, but further improvements are still needed.

Patients and Methods: The aim of this study is to identify the outcome and costs of adult AML patients treated with conventional chemotherapy (CCT) at the National Cancer Institute (NCI), Cairo University during the time period from April 1999 to January 2002. Clinical, laboratory characteristics were all recorded. Data regarding different types of therapies given for these patients including response, outcome and costs were also collected.

Results: The median age of 82 identified AML patients was 34 years. The complete remission (CR) rate after induction with CCT was 52% (42/82 patients) with a median CR duration of 9 months. Twenty-eight percent of patients who achieved CR subsequently relapsed. By January 2003, fifty-eight patients were dead (70.7%). Infections were the major mortality cause, followed by disease progression then bleeding (65%, 28% and 7% respectively). The median treatment cost per patient was 33158 Egyptian Pounds (LE). It was higher for patients who achieved CR compared to those who relapsed and/or died. Drugs contributed by 78 % to the total treatment cost, while hospitalization, investigations and blood-component therapy contributed by 6%, 7% and 8% respectively.

Conclusions: Outcome of patients with AML treated at NCI- Cairo University can be enhanced by improvement of supportive therapy; mainly infection control and expanding BMT programs to accommodate all eligible patients.

Key Words: AML – Chemotherapy – Mortality – Cost – Outcome – NCI – Egypt.

INTRODUCTION

Even though generally considered as an illness of the developed countries, cancer is a world-wide health problem. In the year 2000, 54% of new cancer cases occurred in developing countries [1]. In USA, acute myeloid leukemia (AML) constituted 13410 out of 1444920 (0.9%) new cancer cases diagnosed in 2007. AML led to death in 8990 out of 559650 total cancer deaths [2]. In the National Cancer Institute (NCI) Cairo University during the year 2002, out of a total of 19405 new cancer cases, 169 patients (1.8%) were diagnosed as AML [3].

AML represents a group of clonal hematopoietic stem cell disorders in which both failure to differentiate and over-proliferation of the stem cell compartment result in accumulation of non-functional myeloblasts, impaired hematopoiesis and cytopenias. While the specific cause in any individual patient is usually unknown, the growing understanding of the genetic backgrounds of leukemia is beginning to lead to a wide array of targeted therapies [4].

French-American-British (FAB) classification remains useful in identifying certain biologic subtypes but does not account for all subtypes. More recently, the diagnosis and prognosis of AML is based not only on the FAB classification, but also on cytogenetics, immunophenotyping (IPT) and molecular genetics. Such advances have led to a new World Health Organization (WHO) classification that attempts to correlate morphology, cytochemistry, immu-

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nophenotype, karyotype, and molecular genetics with clinical features [5]. Several host-related and disease-related factors have prognostic importance including age older than 60 years, the presence of an antecedent myelodysplastic syndrome, elevated white blood cell count, karyotype and expression of the multidrug resistant (MDR) phenotype [6,7].

Despite current optimism, the treatment of AML remains unsatisfactory as most patients will die of their disease. Although the rate of complete remission (CR) after induction chemotherapy has steadily increased over the past 2 decades and post-remission chemotherapy is routinely used, most AML patients experience a relapse, and eventually die of their disease. Barriers to a higher cure rate for AML include drug-resistant disease and treatment toxicity [8]. During the last week in their lives, AML patients experience infection in 71% and bleeding in 44% [9].

For patients with AML, treatment with 7 days of cytarabine (Ara-C) and 3 days of daunorubicin has been a standard remission induction regimen used by the Cancer and Leukemia Group B (CALGB), Eastern Cooperative Oncology Group (ECOG) and others. This regimen produced CR in 62% to 71% of patients. The median overall disease-free survival (DFS) was 0.75 years and the 5-year DFS rate was 22%. The 5-year overall survival (OS) rate ranged from 9% to 33% for patients age < 55 years and from 6% to 13% for patients age 55 years [10,11].

Following achievement of CR, Further intensive treatment is required to prevent recurrence. The treatment options include intensified post-remission chemotherapy and stem cell transplantation (SCT). Allogeneic SCT in first CR has been associated with prolonged survival [12].

The aim of this study is to identify the causes of morbidity and mortality in adult acute myeloid leukemia (AML) patients at NCI-Cairo University and to estimate cost-benefit effectiveness of chemotherapy, accompanying auxiliary therapies including antimicrobials, growth factors and blood component therapy.

PATIENTS AND METHODS

This Retrospective study was conducted in the Medical Oncology department of National Cancer Institute (NCI), Cairo University. Records of all adult AML patients treated with

conventional chemotherapy during the time period from April 1999 to January 2002 were reviewed. The patients were followed till January 2003. Clinical data (history and physical examination) and laboratory as well as imaging studies were all recorded. Data regarding periods of hospital stay, drugs and blood-component therapy including their doses, frequency and duration were also recorded. Responses to induction chemotherapy and their duration, causes of morbidity and mortality and periods of survival were also recorded. The costs of all measures and services offered to those AML patients are listed in Table (1).

Statistical analysis:

SPSS 10.0 for windows was used. Significance was assured at a $p < 0.05$. The duration of survival and median survival times {95% confidence interval (CI)} were estimated according to the Kaplan-Meier method.

Table (1): Cost of measures and services offered to adult AML patients at NCI-Cairo University during the study period (April 1999 to January 2002).

Item	Cost*
Hospital stay/day	30
<i>Blood components:</i>	
Packed RBC's/unit	75
Platelets/6units	200
<i>Laboratory studies:</i>	
Complete blood count	30
Serum biochemistry profile/item	10
Bone marrow aspirate	100
CSF examination	50
Immunophenotyping studies	200
Cytogenetic studies	400
Culture and sensitivity/specimen	30
<i>Imaging studies:</i>	
Chest X-ray	30
Abdominal/pelvic ultrasonography	30
Echocardiogram	50
CT scan of the brain	100
CT scan of the abdomen or chest	200
MRI	250
<i>Drugs:</i>	
Chemotherapy, antimicrobials, growth factors and others	Varied according to market price

*Costs are given in Egyptian pounds (LE), one US dollar = 5.7 LE.

RESULTS

During the time period from April 1999 to January 2002, 82 adults with AML were treated at NCI-Cairo University. They were followed till January 2003. Their ages ranged between 18 and 68 years with a median of 34 years. The

male to female ratio was 1.05:1. The commonest FAB subgroup was M1 followed by M2, M3, M4 and M5. Sixty-three patients (77%) received induction by cytosine arabinoside for 7 days and doxorubicin for 3 days (3+7 regimen), 8 (10%) patients received high-dose cytosine arabinoside and mitoxantrone (HAM regimen) while another 8 (10%) patients with M3 subtype received doxorubicin and all-trans retinoic acid (ATRA). Three (3%) elderly patients received cyclophosphamide, vincristine, cytosine arabinoside and prednisone (COAP regimen) (Table 2).

Response to chemotherapy:

Out of 82 AML patients treated with induction chemotherapy, 42 (51%) patients achieved first complete remission (CR1), 8 (10%) patients were refractory and 32 (39%) patients died very early before evaluation of treatment effect. The duration of CR1 ranged between 1 and 37 months with a median of 9 months. No significant associations between CR1 and age, sex, AML FAB-subtype or the type of first-line chemotherapy were noted.

Ten out of the 42 (24%) patients who achieved CR1 died during consolidation chemotherapy and by January 2003, 20 (48%) patients were in maintained CR1, while 12 (28%) patients relapsed and received second-line chemotherapy and 6 of them achieved a second complete remission (CR2). The likelihood to achieve remission after relapse was more if CR1 lasted more than a year (3 out of 6 patients) when compared to CR1 less than a year (3 out of 8 patients) (Fig. 1).

Mortality:

Out of 82 AML patients, 58 (71%) died during the whole course of the study. 32 (39%) patients died during induction chemotherapy, ten (12%) patients died during consolidation chemotherapy, eight (10%) patients died from primary refractory AML and additional eight (10%) patients died from refractory relapse. The causes of mortality are listed in Table (3).

Survival data:

After a median follow-up of 14.5 weeks, the median overall survival (OS) was 14.5 weeks (95% CI: 8-30 weeks) (Fig. 2). Most of deaths occurred during induction (55%) or shortly after and during consolidation (31%). The median disease-free survival was 1.5 weeks (95% CI: 0-5 weeks) (Fig. 3).

Cost issues:

Costs were calculated once for the whole group (82 patients) and once for those in maintained CR at the end of the study compared to those who died during the study period (Table 4). Drugs were the major contributor to the total cost (78%), while hospitalization, investigations and blood-component therapy contributed by 6%, 7% and 8% respectively.

All these costs (apart from blood component costs) were significantly higher in patients with maintained CR compared to others ($p < 0.001$).

Table (2): Characteristics of the 82 adult AML patients included in the study performed at NCI-Cairo University during the time period from April 1999 to January 2002.

Parameter	Number (%)
Sex:	
Male	42 (51)
Female	40 (49)
Age (years):	
Range	18-68
Median	34
AML subtype:	
M1	39 (48)
M2	27 (33)
M3	8 (10)
M4	6 (7)
M5	2 (2)
Induction chemotherapy regimens:	
(7+3)*	63 (77)
HAM**	8 (10)
Doxorubicin + ATRA***	8 (10)
COAP****	3 (3)

* (7+3) : Cytosine arabinoside for 7 days and doxorubicin for 3 days.

**HAM : High-dose cytosine arabinoside and mitoxantrone.

***ATRA : All trans retinoic acid (for M3).

****COAP: Cyclophosphamide, vincristine, cytosine arabinoside and prednisone (used in old patients with poor general condition).

Table (3): Causes of mortality of adult AML patients included in the study performed at NCI-Cairo University during the time period from April 1999 to January 2002.

Infection in 38/58 (65%) cases:
Bacterial infection in 26/38 (69%) cases
Fungal infection in 10/38 (26%) cases
Viral hepatitis in 2/38 (5%) cases
Disease-related in 16/58 (28%) cases:
Primary refractoriness to chemotherapy in 8 cases.
Relapse after initial response in another 8 cases.
Uncontrollable hemorrhage in 4/58 (7%) cases:
Uncontrolled DIC* (2 cases)
Massive hematemesis (one case)
Severe intracranial hemorrhage (one case)

* DIC: Disseminated intravascular coagulopathy.

Table (4): Costs of treating 82 adult AML patients with conventional chemotherapy at NCI-Cairo University during the time period from April 1999 to January 2002.

Group	Total no AML patients	Death during study	Maintained CR
Number	82	58	24
<i>Hospital stay (days):</i>			
Range	2-270	2-209	33-270
Median	60	37	111
<i>Total cost (LE):</i>			
Range	410-106100	410-85473	21005-106100
Median	33158	23244	46218
<i>Hospital stay cost (LE):</i>			
Range	60-8100	60-6270	990-8100
Median	1800	1110	3330
<i>Drug cost (LE):</i>			
Range	150-85365	150-67460	16390-85365
Median	26448	17453	36833
<i>Blood components cost (LE):</i>			
Range	0-8110	0-8110	625-8050
Median	2388	2125	3050
<i>Investigations' cost (LE):</i>			
Range	200-8225	200-6625	400-8225
Median	2238	1315	3816

*Costs are given in Egyptian pounds (LE), one US dollar = 5.7 LE.

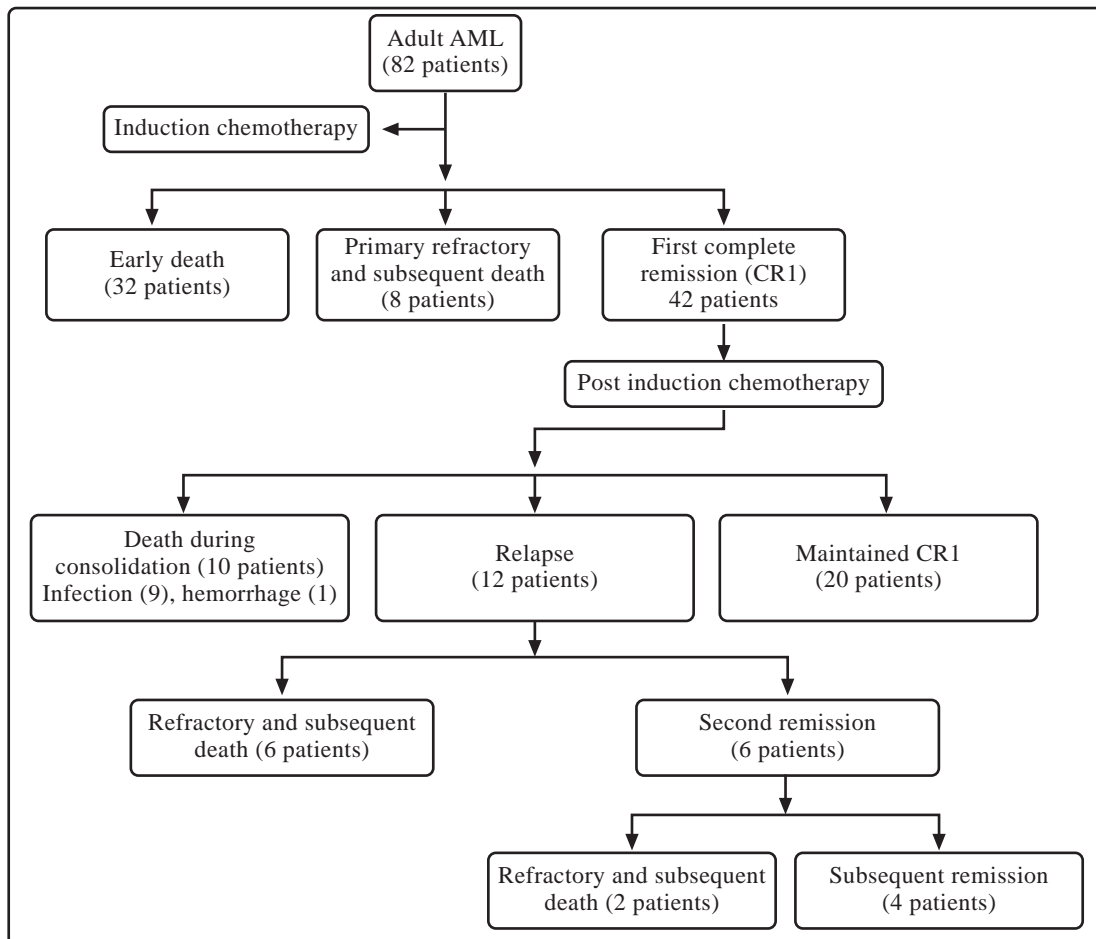


Fig. (1): Response to chemotherapy in the 82 adult AML patients included in the study performed at NCI-Cairo University during the time period from April 1999 to January 2002.

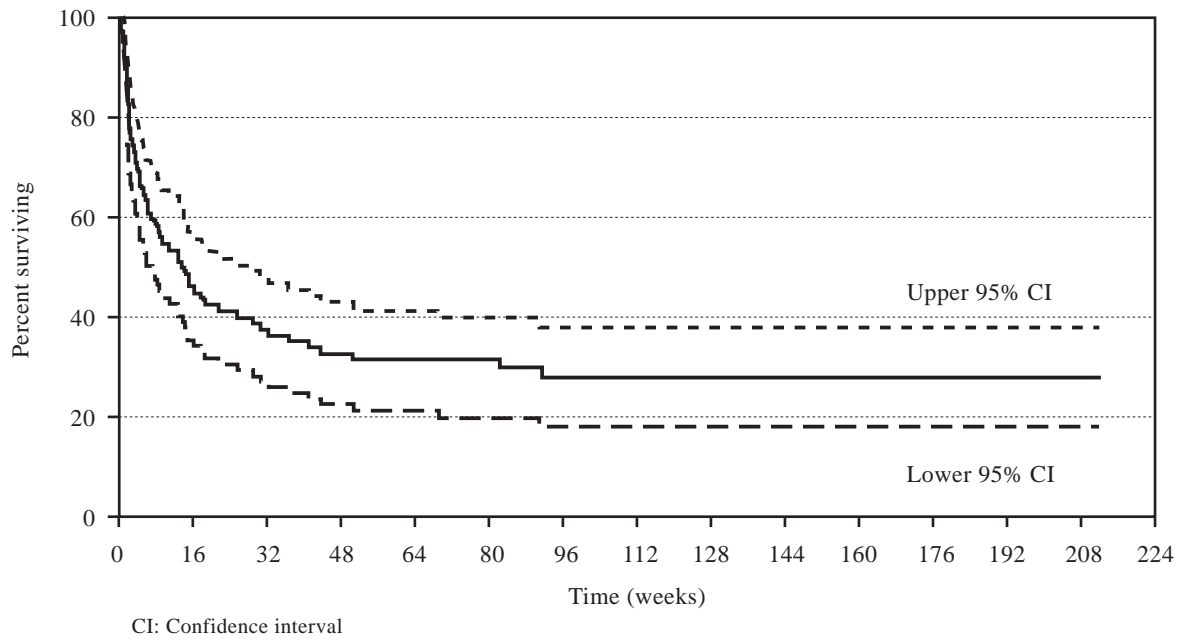


Fig. (2): Overall survival of the 82 adult AML patients included in the study performed at NCI-Cairo University during the time period from April 1999 to January 2002.

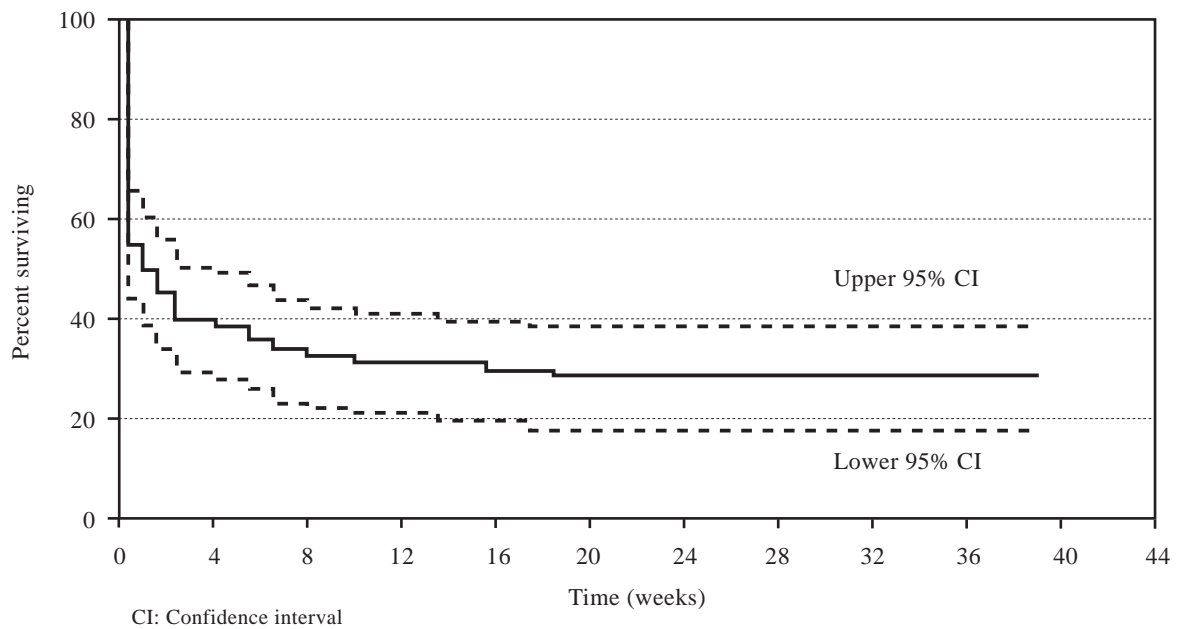


Fig. (3): Disease-free survival of the 82 adult AML patients included in the study performed at NCI-Cairo University during the time period from April 1999 to January 2002.

DISCUSSION

In our study, the median age (34 years) as well as male predominance (51%) were comparable to previous studies from NCI-Cairo University by Hamza et al. [13,14] and El Serafi et al. [15]. In contrast, studies from Western countries denote that the median age at time of AML

diagnosis is 64 years [16]. This can be due to higher proportion of elderly in the Western population compared to that in Egypt.

In our study, all cases were diagnosed and subtyped according to the FAB classification [17,18], based on morphological and cytochemical characteristics. The frequencies of M2, M3

and M5 subtypes in our study were comparable to what is reported by Koeffler [19]; Grignani et al. [20] and Nucifora and Rowley [21]. None of the patients included in this study were categorized as having M0, M6, or M7. We reported a frequency of AML M1 that is twice that reported by Hematologique [22]. The frequency of AML M4 in our study was half that reported by Koeffler [19]. Immunophenotyping (IPT) was done only for 40/82 (49%) patients, so many cases who could have been diagnosed M0, M6 or M7 were classified on the basis of morphology and cytochemistry as M1 leading to a higher frequency as compared to others. Also lower frequency of AML M4 can be explained by lack of IPT which if available could have shifted some M1 cases to be M4. In support of our explanation, 10/40 (25%) cases studied by IPT were originally classified by morphology & cytochemistry as M1 or M2 and upon positivity for CD14 were shifted to M4/M5. Similar data were observed by El Serafi et al. [15] and Farahat, et al. [23].

Forty-two patients (51%) achieved complete remission (CR1) with induction chemotherapy. The median time of CR1 was 9 months. Twelve out of the 42 (28%) CR1 patients relapsed. The likelihood to achieve a second CR was higher in patients with CR1 duration of more than one year compared to less than a year (75% versus 37% respectively). Our CR1 rate was lower than the 62% rate reported by Bennett et al. [10]. This can be explained by the higher proportion of early deaths in our study. Our CR1 duration was lower than the 12 months reported by Wahlin et al. [24]. The anthracycline we used was doxorubicin rather than daunorubicin that was used by Wahlin et al. [24], which may explain the difference.

Out of the 82 AML adult patients included, 58 patients died during the study period (70.7%) and only 24 patients were alive at its end (29%). Bennett et al. [10] reported that out of 1400 new AML patients treated with conventional chemotherapy, 76% had relapsed or died and the overall survival rate at 5 years was 15%. Our figures are slightly higher taking in consideration the shorter period of follow-up and the smaller number of patients in our study.

Infection was the major cause of mortality (65%), while resistant or relapsed disease led to death in 16 (28%) patients. Uncontrolled

bleeding caused 7% of the mortalities. This correlated with figures reported by Rees et al. [25]; and El Serafi et al. [15].

The median days of hospitalization were 60 days. Hospital stay was shorter for patients who died than those who maintained disease remission (37 versus 111 days).

In our study, the median total cost of therapy per patient was 33158 LE. It was higher for those who maintained disease remission (46218 LE) compared to those who died during the study (23244 LE). The median cost of bone marrow transplantation (BMT) in NCI-Cairo University is 83815 LE. Taking in consideration the superior outcome of high dose therapy and BMT in AML in CR1 and also the small absolute difference in the total cost between BMT and conventional chemotherapy, we highly recommend further support of the BMT program to be able to cover eligible AML patients in CR.

The median total treatment cost in this study (33158 LE) is far below what is reported by Dufour et al. [26] (304846 French Francs) (189000 LE) and by Nordmann et al. [27] (107592 Swiss Francs) (225943 LE), while the median cost of one course of induction chemotherapy in USA is \$16701 (95195 LE) [28].

Drugs contributed by 78% to the total treatment cost, while hospitalization, investigations and blood-component therapy contributed by 6%, 7% and 8% respectively. The main difference in cost relates to a very lower cost of hospitalization and manpower in Egypt. Also the cost of blood-component therapy and investigations are lower in Egypt compared to the Western countries. In our study, the median cost of blood components used was LE 2388 in comparison to \$11406 (65014 LE) reported by Balducci et al. [29].

Recommendations:

A better outcome of Egyptian adult AML patients, comparable to what is reported in Western countries, can be achieved with a far lower cost. IPT and cytogenetics should be incorporated in initial diagnostic workup of AML patients. Improvement of supportive therapy with special emphasis on infection control is urgently needed. Egyptian BMT programs should be expanded and supported to accommodate all eligible AML patients.

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