Outcome of Induction Therapy in Adult Patients with Acute Myeloid Leukemia

Alaadin Sahham Naji

ABSTRACT:

BACKGROUND:

Treatment of patients with newly diagnosed acute myeloid leukemia (AML) has improved during the past decades due to the intensification of induction and post remission chemotherapies and due to the incorporation of autologous and allogeneic transplantation procedures. Untreated acute leukemia is a uniformly fatal disease with a median survival time shorter than 3 months.

OBJECTIVE:

To evaluate the outcome of induction and complications post induction in adult patients with Acute Myeloid Leukemia(AML) in Baghdad Teaching Hospital

PATIENTS AND METHODS:

A total of 47 patients diagnosed as de novo AML who had been admitted within twelve months from January till December 2012 in hematology unit of Baghdad Teaching Hospital were included. Treatment of the 47 eligible patients for remission induction with standard intensive treatment course consisted of the combination with standard-dose cytosine arabinoside 100 mg/m2/d continuous infusion on days 1-7, with of doxorubicin in a dose of 30mg/m2 over half an hour infusion on day 1-3.Response to therapy was assessed for complete remission or persistence of leukemic cell post induction**.** Pattern and severity of infections and their relationship with granulocytopenia. were analyzed.

RESULTS:

The patients had a mean age of of 36.7 years ranged from 14 to 72 years. Performance status in 15 patients was 0 or I while the majority (43) patients was with PS of II-IV at diagnosis according to WHO/ECOG performance status scale. Duration between symptoms of AML prior diagnosis till suspicion of a diagnosis of AML at a referring hospital and confirmation of the diagnosis at our institute have been assessed with(mean +SD) duration 32±22.1days.

of the 47 patients 22(47%) achieved complete remission post first induction (CR1)and further 5(11%) patients have CR2(after second remission) and 20(42%) was refractory to treatment. Focus of infection during marrow hypoplasia have been identified in 26(59%) patients.

CONCLUSION:

Based on the current data ,the remission rate was nearly comparable to the results with other reports . Intensification of anthracyclins and identification of cytogenetic and other independent prognostic relevance are needed to obtain better results.

KEY WORD: acute myeloid leukemia, induction outcome.

INTRODUCTION:

Standard induction therapy for patients with AML, consisting of daunorubicin and ara-C in conventional doses, results in a complete remission (CR) rate of 50-60% in an unselected population and a long-term survival of about 10-20%. The speed and the morphological response to the first induction course are predictive for relapse [(1)].

Induction therapy for acute leukemia is treatment intended to achieved complete remission (CR). Complete remission is defined as the absence of morphologic evidence of leukemia after recovery of the peripheral blood cell counts. Failure to achieve CR may be attributed to death during chemotherapy-induced bone marrow hypoplasia or to drug resistance manifested either as failure to achieve hypoplasia or as persistent leukemia after recovery from hypoplasia[(2)].

It is well established that age at the time of diagnosis, leukemia cell karyotype, and whether the leukemia is de novo or secondary are factors that influence treatment decisions. Patients with favorable prognostic factors should probably receive conventional therapy. Patients with unfavorable prognostic factors have shown little benefit from conventional therapy Mortality

Baghdad Medical College/Baghdad Teaching Hospital.

during induction therapy is correlated with age and, perhaps, leukocyte count [3].

Patients who have persistent leukemia after the first course of induction chemotherapy generally are given a second course of the same drugs. The patient's long-term outcome is worse if two courses of treatment are required even if a complete remission is achieved. Approximately 40 percent of patients with persistent AML after one course of induction therapy have a complete remission after a second course and disease-free survival at 5 years is approximately 10 percent[4].

PATIENTS AND METHODS:

A total 47 patients as de novo AML who were assigned and collected prospectively(six of them had been captured retrospectively) within twelve months from January till December 2012 in single institute of Baghdad Teaching Hospital. Treatment of 47 of these patients for remission induction with standard intensive treatment course consisted of the combination with standard-dose cytosine arabinoside 100 mg/m2/d continuous infusion on days 1-7, in a dose of 30mg/m2 of doxorubicin on half hour infusion on day 1-3 followed by a period of supportive care .

Patients were collected to assess state of remission post first and second course of induction .Patients with newly diagnosed de novo AML were eligible for treatment .However ,older patients than 65 years were included if they have good performance status without comorbid illiness. Patients with acute promyelocytic leukemia , patients with severe comorbidity precluding the initiation of intensive induction chemotherapy have been excluded.

Cytomorphologic assessment was based on histochemical stain with Sudan Black and Peroidic Acid Schiff were used,and in those cases the cytomorphology not solved the diagnosis,Flowcytometry or immune - histochemical was used as a tool for diagnosis in these cases. AML cases were classified Cytomorphologically according to the criteria of the French-American-British (FAB) classification[5] .

Assessment of residual bone marrow blast cells on day14 post completion of chemotherapy and upon full recovery of peripheral blood counts.

During the neutropenic period all these patients have been supported with blood component and antibiotic therapy and the site of infection tried to identified in those patients who were defined to have febrile episodes, although microbiological documentation to the causative organisms are not included in this study. Complications rather than infection had been also documented and graded by common toxicity criteria. Duration of hospitalization since admission of the patients till time of discharge had been recorded in this study.

Response to therapy was assessed according to Cancer and Leukemia Group B (CALGB) criteria[6]. Complete remission (CR) was defined by a bone marrow with normal hematopoiesis of all cell lines, fewer than 5%blast cells, and a peripheral blood with at least 1500/µL neutrophils and 100 000/µL platelets. Therapeutic failures were classified as persistent leukemia

Statistics by SPSS using descriptive and regression analysis were performed to evaluate frequency ,mean, standard deviations(SD) and the dependence of the variables CR, day 14 post completion of therapy, as a continuous variable with other prognostic variables .A P value of <0.5 was considered indication of statically significance difference.

RESULTS:

A total of 47 patients were assigned as AML were exposed and eligible for induction course with intensified therapy. Patients had a mean±SD age36.7±14.8 years ranged from 14 to 72 years and the ratio of male-to-female was 1.5:1.0. The characteristics of the patients treated are presented in table (1)

Performance status (PS) according to WHO/ECOG performance status scale at the time of diagnosis was 0 or I in 15 of these patients while the majority(42)patients with PS II-IV at diagnosis Minimum and maximum duration of hospitalization was calculated with mean duration of hospitalization was 29.7days .

In nine(19%) cases diagnosis was based morphologically as myeloblastic leukemia without subtyping ,and the other cases we found that FAB type *M2* or WHO designation AML with maturation is the most frequent type , as this variant is 49% percent of AML cases; thus, approximately 62% percent of cases of AML are myeloblastic leukemia with or without maturation,while monocytes represent less than 11 percent of cells and 6%erythroblastic and no case of megakaryoblastic has been registered .

Mean duration between starting of the symptoms and referral to our center was 32 days which reflect the long delay of patients referral to our institute and later on a delay in starting therapy .

Dysplastic features have been found in 8(17%) patients, all of them not responding to treatment, only one showed response and his cytogenetic study showed good cytogenetic with chromosomal inv16 .presence of dysplastic feature significantly correlate with poor response to induction therapy (p-value 0.03).

In this study leucocytosis(>30X10^9/L) recorded in16(34%) patients and leucopenia (<4X10^9/L) which documented in 13 (28%) patients however, both in this study not correlate significantly with remission outcome respectively(p-value 0.75,0.532).

Table 1: Characteristicsof 47 adult patients with de novo AML.

Age(years) Range Mean+SD	 14-72 36.7±14.8
Male :female ratio	1.5:1.0
Duration of symptoms prior admission(days) Mean+SD Range	 32 days+22.1 4-84
Performance status(ECOG) Score 0 Score 1 Score 2 Score 3 Score 4	 2 (4%) 13(28%) 15(32%) 14(30%) 4 (8%)
Subtype of AML M1 M2 M4 M5 M6 M7 Myeloblastic without subtyping	 6 (13%) 23(49%) 1 (2%) 5 (11%) 3 (6%) 0 9(19%)
Presence of dysplastic morphology	8(17%)
White blood at presentation(X10^9/L) (mean +SD) median Range	 42.2+33.3 10 0.5-225
Percentage of peripheral blast(%) Mean+SD range	 40.5+35.1 (0-98%)
Duration of hospitalization(days) Mean+SD Range	 29.7+10.8 18-60

Prior to therapy all patients clinical manifestations had been documented with anemia was the commonest symptoms followed by fever . Sixteen patients have splenomegaly which found not significantly correlated with remission(p-value 0.737).

Table 2: Frequency of clinical presentation in AML patients.

Symptoms	No.	%
Anemia	30	64
Fever	24	51
Vomiting and diarrhea	2	4
Weight loss	7	15
Bone pain	2	4
Post surgery fever and bleeding	3	6
Purpuric rash	12	25
Vaginal bleeding	4	8
Epistaxsis	2	4
Retinal hemorrhage	1	2
Gum bleeding	2	4
Upper gastrointestinal bleeding	2	4
Jaundice	4	8
Deep vein thrombosis	1	2
Subcutaneous nodule	1	2
History of blood transfusion at presentation	4	8
Infection Canula infection Chest infection	 2 3	 4 6
Gum hypertrophy	2	4
Lymphadenopathy	9	19
Vasculitis	1	2
Serositis(pleural and ascitis)	1	2
Splenomegaly	16	34
Hepatomegaly	10	21

Treatment outcome of all 47 patients, 22 (47%) achieved CR1(after first induction course), and further 5 (11%) achieve CR2 (after second induction) . Table (3)

Table 3: Response to induction by conventional therapy.

Response to conventional therapy	No.	%
Complete remission from first cycle	22/47	47
Complete remission from second cycle	5/47	11
Persistent leukemia	20/47	42

All patients had neutropenic fever (grade III) post induction with documented site of infection in26 patient while the remainder no focus of infection had been detected. Data have been available only for 41 patients. Table(4)

Table 4 : Sites of infection clinically evident post induction as a complication of aplasia

Site of infection	Number of patients	%
Perianal cellulitis	7	17
Gluteal abscess	2	4
Lower limb cellulitis	2	4
Vaginal discharge	1	2
Gastroenteritis	3	7
Sinus infection	2	4
Chest infection	3	7
Testicular swelling and infection	1	2
Phlebitis	5	12
	26/41	59%

Other complications that happened during and post chemotherapy.Table(5)

Table 5 : Complications other than infections that occurred in these patients.

complication	Grade 1	%	Grad e2	%	Grade 3	%	Grade 4	%
Nausea	3	7%	4	10%	2	4%	0	0
Vomiting	5	12%	4	10%	2	4%	0	0
Constipation	0	0	1	2%	2	4%	0	0
Dysphagia	2	4%	2	4%	2	4%	0	0
Stomatitis	3	7%	4	10%	1	2%	0	0
bleeding								
Haematuria	0	0	1	2%	0	0	0	0
Epistaxis	0	0	0	0	0	0	2	4%
Retinal	1	2%	0	0	0	0	0	0
Vaginal	0	0	0	0	3	7%	2	4%
↑ serum bilirubine	0	0	1	2%	1	2%	1	2%
↑serum creatinin	1	2%	0	0	1	2%	1	2%

Variables that affect the complete remission,non of them in this study found to affect significantly the outcome apart from presence of dysplastic feature.Table(6)

Table 6:Correlation between different variables and response to induction therapy.

Variable	N0.	Responding to chemotherapy	Not responding	P value
Presence of dysplastic morphology	8	1	7	***0.03***
Leukocytosis(> 30x109/l)	16	8	8	0.75
Leucopenia(<4X109/l)	13	6	7	0.53
Presence of splenomegaly	18	9	9	0.73
Age >55 years	5	1	4	0.27
Duration of symptoms >30 days	16	9	7	0.36

DISCUSSION:

As acute myeloid leukemia (AML) is considered an oncologic emergency, the presumed need to begin treatment immediately and time effect of starting early therapy examined by Mikkael et.al, determine the effect of time from AML diagnosis to treatment on complete remission (CR) and overall survival (OS) by using other patients characteristics available at diagnosis with longer time was associated with worse CR and OS in younger but not older patients [(7)].

Although it is not significantly correlated with remission in this study the median time from starting symptoms and diagnosis at an out-side facility or referral from other centers to date of start treatment in our institute was 32 days. This frequent delay implies that, in many cases, although mostly unavoidable, is the main reason for delay provided the patient himself is the reason because of the un awareness about the symptoms and the disease and lack of the facilities to diagnose the disease, and lastly because majority of our patients present with poor performance status made them needs more time to support them before starting therapy.

Many studies have focus on leukemic cell masses as prognostic relevance with white blood cell at presentation. Acute myeloid leukemia (AML) presenting with a high leukocyte count has been associated with an increase in induction mortality and poor results in a number of other survival measures(8).In the contrary, clinical significance of leukopenia at the time of diagnosis had no effects on CR and carries no prognostic significance in AML [(9)].Our results did not showed any significance impact related to leukocyte count which may be due small sample number.

The prognostic relevance of the dysplastic features for patients with de novo AML remains unclear. However, The presence of dysplastic morphology effect inversely and significantly in response of our patients. Kahl C et al evaluate the role of dysplasia in de novo AML, 26.0% of them showed trilineage dysplastic features. A significantly worse prognosis was calculated for those patients with detection of dysplasia compared with patients without any dysplastic sign [(10)].

Organomegally and lymphadeopathy have been reported in some studies have a negative impact on attainment of CR as it is possible that the spleen might represent a sanctuary site of the disease[(11)].

In this study ,presence of splenomegaly not significantly correlate with response to therapy despite still half of them responding to treatment even in those with poor prognostic morphology.

Our results showing that 22(47%) of patients who received induction achieved CR1 further 5(11%) patient achieve CR2with overall CR 58% .despite, all patients achieve CR2 relapsed. Our results seems comparable to other results of several large studies which indicate that approximately 60% to 70% of AML patients with intermediate-risk cytogenetics, can achieve CR with standard induction chemotherapy using daunorubcin dosage 45mg/m2 and results of the remission rate was higher by *Sherif S. Farag* et al showing that 73% of karyotypically normal patients achieved CR.[11]

Patient not attain remission from first induction sill can responding to second course despite they are prognostically poorer than CR1.The second course will convert half of the remainder so that this raised the percentage of CR to 70-75% [12] .

Our results of remission looks comparable to other results and we may have better remission rate if we put in our consideration use of daunorubicin, idarubicin, or mitoxantrone rather than doxorubicin as daunorubicin remain the standard of care in many randomized trials especially escalation or intensification of the dose.

The importance of risk stratification into broad prognostic groups with cytogenetic commonly used to guide post remission and identify subtype suited to specific therapy and this is done only in three patients for good cytogenetic which proved to be positive for inv[16]and the other one was negative, they achieved remission and they expected to have long-lasting remissions[13].

As the initial goal of the therapy is induction of CR, which usually required period of hypoplasia (except acute promyelocytic leukemia) with increase risk of infection.Our results showed the focus of infection could be determine in 59% of the patients as source of fever ,still 41% no site of infection had been detected however, no data available regarding the microbiology. Results by Kumar et al where infections could be documented microbiologically in 58.2% and clinically in 30.0% of episodes. In the remaining 41.8% of episodes, no clinical, radiological or microbiological evidence could be found out[14].

and with improvement of supportive therapy including transfusion support and empirical antibacterial and antifungal and availability of growth factors, the later has become less significant and this is what is translated in this study where early death(during induction period and hypoplasia) only three deaths had happened in the remission rate was nearly comparable to the results with other reports despite still type and intensified dose of daunorubcin or idarubicin not included in our patients. Intensification of anthracyclins and identification of cytogenetic and other independent prognostic relevance in larger number of patient needs to incorporated together to give better results for Iraqi patients with AML along with improvement of supportive care facilities.

REFERENCE:

1. Kimby E, Nygren P, Glimelius B. A systematic overview of chemotherapy effects in acute myeloid leukaemia. Acta Oncol. 2001;40:231-52.
2. Cripe LD. Adult acute leukemia. Curr Probl Cancer. 1997;21:1-64.
3. Greenwood MJ, Seftel MD, Richardson C, et al: Leukocyte count as a predictor of death during remission induction in acute myeloid leukemia. *Leuk Lymphoma*.2006; 47:1245 [PMID: 16923553]
4. Schlenk RF, Benner A, Hartmann F, et al: Risk-adapted postremission therapy in acute myeloid leukemia: Results of the German multicenter AML HD93 treatment trial. *Leuk Res* 2003;17:1521,. [PMID: 12886238]
5. Bennett JM, Catovsky D, Daniel MT, et al. Proposed revised criteria for the classification of
6. acute myeloid leukemia: a report of the French-American-British Cooperative Group. Ann Intern Med. 1985;103:620-25.
7. Mayer RJ, Davis RB, Schiffer CA, et al. Intensive postremission chemotherapy in adults with acute myeloid leukemia: Cancer and Leukemia Group B. N Engl J Med. 1994;331:896-903.
8. Mikkeal A Sekeres,Paul Elson,Matt E Kalaycio.Time from diagnosis to treatment initiation predicts survival in younger, but not older, acute myeloid leukemia patients Blood . 2009 ;113:128-36.
9. Greenwood MJ, Seftel MD, Richardson C, et al: Leukocyte count as a predictor of death during remission induction in acute myeloid leukemia. *Leuk Lymphoma* . 2006;47:1245. [PMID: 16923553]
10. Arellano M, Bernal-Mizrachi L, Pan L. Prognostic significance of leukopenia at the time of diagnosis in acute myeloid leukemia. Clin Lymphoma Myeloma Leuk. 2011;11:42 7-32.

11. Kahl C, Florschü tz A, Müller G, et al: Prognostic significance of dysplastic features of hematopoiesis in patients with de novo acute myelogenous leukemia. *Ann Hematol*.1997;75:91. [PMID: 9368477].

12. Sherif S. Farag, Amy S. Ruppert, Krzysztof Mrózek. Outcome of Induction and Postremission Therapy in Younger Adults With Acute Myeloid Leukemia With Normal Karyotype: A Cancer and Leukemia Group B Study.journal of clinical Oncolojy. 2005;23:3482-93.

13. Burnett AK,Wetzler M,Lowenberg B.Theraputic advance in acute myeloid leukemia .J Clin Oncol.2011;29:487-94.

14. Grimwade D, Walker H, Oliver F, et al. The importance of diagnostic cytogenetics on outcome in AML: analysis of 1612 patients entered into the MRC AML 10 trial. The Medical Research Council Adult and Children's Leukaemia Working Parties.Blood. 1998;92:2322-33.

15. Kumar L, Kochupillai V, Bhujwala RA. Infections in acute myeloid leukemia. Study of 184 febrile episodes. J Assoc Physicians India. 1992;40:18-20.