The use of modified MidAC regimen in the treatment of adult patients with de novo Acute Myeloid Leukemia in Baghdad Teaching Hospital

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Abstract:

Background: Consolidation chemotherapy is an important concern in maintaining remission in acute myeloid leukemia (AML) .

Objectives: We intended to evaluate the efficacy of using modified MidAC regimen in the therapy of adult AML patients .

Patients & Methods :Twenty-six patients (mean age, 25 years; range, 17 to 45 years) with de novo AML were given induction regimen according to the AML subtype .Patients who failed induction, were received modified MidAC as salvage therapy .All patients who achieved complete remission (CR) were assigned to receive 3 successive courses of modified MidAC as a consolidation treatment .

Results :A total of 21 (80%) patients went into CR after one induction regimen .In the rest 5 (20%), 3 (60)%of them enter CR after re-induction with modified MidAC, and 2 (40)%died .Total 24 patients assigned for consolidation therapy .After completing the 3 consolidation courses, 21 (88)%of them were maintained in remission while 3 (12 %)died .The median duration of follow up was 11.7 months .At the end of the study, 13 patients) 54)%were in CR and 8 (38)%relapsed .The median overall survival) OS)is 20 months and the 2 years OS is 41.%Median disease-free survival (DFS)is 17 months and the 2 years DFS is 37 .%Median survival after relapse was 2.5 months .Main toxicities after modified MidAC regimen were myelosuppression, GIT complications and sepsis .

Conclusion :Modified MidAC regimen is an option as a consolidation or as a salvage therapy in the treatment of adult AML patients with minimal difference in the rate of toxicity when compared with other high-dose regimens .

Key words: AML treatment, consolidation, MidAC

Introduction

Acute myeloid leukemia (AML) is a heterogeneous group of diseases characterized by uncontrolled proliferation of clonal neoplastic hematopoietic precursor cells and impaired production of normal hematopoietic leading to neutropenia, anemia, and thrombocytopenia.[1].

AML occurs at any age, but is more common in adults, with increased frequency as age advances . In the United States, the overall annual incidence is 3.4/100,000.[2]AML accounts for 80-90 %of cases of acute leukemia in adults, while it accounts for less than 15 %of cases of leukemia in children younger than 10 years of age.[3]

Therapy of AML can be divided into two phases : induction and consolidation .

The goal of induction chemotherapy is to empty the bone marrow of all hematopoietic elements(both benign and malignant) and to allow repopulation of the marrow with normal cells, thereby yielding remission(<5 %marrow blasts.).

The standard regimen of induction phase for all AML subtypes except M3 AML is cytarabine 100mg/m[2] per day by continuous infusion for 7 days and daunorubicin 45-60mg/m^2 per day intravenously for 3 days.[4,5]

Additional cytotoxic therapy after a successful remission induction is mandatory in order to eradicate the residual disease.Increasing the intensity of consolidation treatment is beneficial in younger but not older adults [6] .In an Eastern Cooperative Oncology Group (ECOG) trial of patients in first CR, there was improved DFS for those who received high-dose versus those who received maintenance therapy[7] .The Cancer and Leukemia Group B (CALGB) study showed improved DFS in patients received high-dose regimen than the intermediate or low dose Ara-C regimen[8].In AML15 trial, the consolidation regimens (MidAC)were also effective, and results were similar to the use of high dose Ara-C for good risk patients[9] .

This study is designed for evaluation of the response rate and duration of response of modified MidAC regimen as a consolidation therapy or as salvage reinduction therapy in patients with AML as well as toxicity and mortality rate .

Patients & Method:

Twenty six patients with diagnosis of AML were given modified MidAC regimen between March 2006 and August 2008 in the department of hematology in Baghdad Teaching Hospital . Diagnosis of AML was established in the Teaching Laboratories according to the cytomorphology and criteria of the French-American-British (FAB) classification system. Modified MidAC regimen was given for two groups of patients :

1-Newly diagnosed AML patients, who achieved a CR after initial induction course, were given 3 courses of modified MidAC protocol, 28 days apart, as a consolidation treatment .

2-Newly diagnosed AML patients, who didn't achieve CR after the 1st induction course, were given modified MidAC regimen as a 2nd line induction therapy .

After explanation to the patient and/or the family, a written consent was taken .

Patients with the following characteristics were excluded from the study :

1-Age >50 years .

2-ECOG (Eastern Cooperative oncology Group) performance status >2 .

3-Significant organ dysfunction :

a-Creatinine>2 ×normal

b-Alanine aminotransferase (ALT)>2 × normal

c-Cardiac ejection fraction < 60 %

Treatment

For FAB groups M1, M2, M4, and M5, induction therapy consisted of:

1-Doxorubicin 30mg/m^2 per day i.v .infusion over 30 min from Day 1-3 .

2-Cytosine arabinoside 100mg/m^2 per day i.v . infusion over 16 hours from Day 1-7 .

For FAB group M3, doxorubicin 30mg/m^2 per day i.v .infusion over 30 min was given on days 1, 3, 5, 7 (4 doses)along with ATRA in a dose of 45mg/m^2 PO daily in 2 divided doses from day 1 till remission.

Other supportive measures provided for the patients during treatment were nystatin oral drops, chlorhexidine mouth wash, fluconazole 150mg PO daily, ciprofloxacin 500mg PO twice per day, ranitidine 150mg PO twice per day and allopurinol 300mg PO daily .Platelet transfusion is given in case of bleeding tendency or platelet count less than 20 $\times 10^9$/L .Blood transfusion is given to maintain hematocrit above 25%.

Patients with M3 AML were also supported by giving them fresh frozen plasma (FFP) and

cryoprecipitate daily till normalization of the coagulation profile .Dexamethasone was also given to prevent ATRA syndrome in a dose of 4mg i.v . every 8 hours daily and tapered gradually after 2-3 weeks from the start of induction .

Empiric broad spectrum antibiotics were started to prevent or control sepsis in case of fever >38° C lasting more than 1 hour, or single reading >38.5° C.

Evaluation and Criteria for Response

Bone marrow aspirate was obtained 2-3 weeks after completion of induction therapy of 3&7, and 4-6 weeks after starting ATRA and chemotherapy in case of M3 AML .

Complete remission (CR)was defined as no circulatory blasts, with ANC >1.5 $\times 10^9$/L, and platelet count >100$\times 10^9$/L and cellular marrow with blasts <5 % and absence of extramedullary disease .

Partial response (PR) was defined as at least 50 % reduction in marrow blast percent from the initial presenting count .

Failure of induction was defined as less than 50 % reduction in marrow blast percent from that at presentation, with early death (death before completion of chemotherapy regimen), or hypoplastic death(death after the completion of chemotherapy regimen, and before hematological recovery).

Relapse was defined as presence of >5 %blasts in the marrow after initial achievement of CR .

Modified MidAC regimen was given as consolidation therapy for patients in CR as three courses, 28 days apart, or given as reinduction salvage therapy for patients with PR or after failure of induction .

Modified MidAC course consisted of mitoxantrone 8mg/m[2](or doxorubicin 30mg/m^2) i.v .30 min infusion daily for 2 days, and Ara-C (cytarabine)1g/m[2]i.v .3hours infusion twice daily for 3 days for 6 doses .

Prophylactic oral antifungals and antibiotics like in the induction phase were given in addition to dexamethasone eye drops every 6 hours to prevent conjunctivitis .

Subsequent MidAC courses were given after one month providing there is hematological recovery) i.e .WBC count >3$\times 10^9$/L, and platelet count >100 $\times 10^9$/L) .

After completion of 3 courses of consolidation therapy, bone marrow aspirate and biopsy were done for evaluation of response and patients who still running CR were seen regularly every 1-2 months for follow up .Toxicity was graded according to the common toxicity criteria of the National Cancer Institute.[10]

Statistical Analyses

Endpoints considered in the data analysis were as follows :

(a)CR

(b)Overall survival OS (calculated from the first day of diagnosis until death or end of follow-up; censored observations occurred only at the end of follow-up);

(c)Disease-free survival (calculated from the first day of CR to relapse, death, or the end of follow-up; censored observations occurred only at the end of follow-up without relapse)

Disease-free and overall survival were estimated by the Kaplan-Meier method.[11]

The Results

The patients' characteristics

Twenty six patients with mean age of 25 years (range 17-45) were included in the study, 11(42)% of them were males .Nineteen patients (73%) present with anemia, 11 (42%) had infection, and 13 (50%) had palpable spleen at the time of presentation **(table 1). Figure 1** shows the study design .

Table 1: The characteristics of the patients

Parameters	No .of patients	(%)
Age (years)		
Mean	25	
Range	17-45	
<20	4	15
20-29	15	58
30-40	5	19
>40	2	8
Gender		
Males	11	42
Females	15	58
FAB Classification		
M1	4	15
M2	4	15
M3	14	54
M4	3	12
M5	1	4
Presentation		
Anemia (PCV <30)	19	73
WBC <2 ×109/L	4	15
WBC >20 ×109/L	5	19
Infection	11	42
Bleeding	11	42
Splenomegaly	13	50

Table 2: Results of salvage therapy using modified MidAC regimen

	No .of patients	(%)
CR	3	60
Death	2	40
Total	5	100

Table 3: Toxicity of modified MidAC regimen as salvage therapy

	Grade 2 (%)	Grade 3 or 4 (%)
Anemia	3 (60)	0
Leucopenia	2 (40)	2 (40)
Thrombocytopenia	0	0
Bleeding	2 (40)	0
Fever	3 (60)	1 (20)
Nausea & vomiting	3(60)	2 (40)
Stomatitis	3 (60)	2 (40)
Diarrhea	3 (60)	1 (20)
Conjunctivitis	0	0
CNS toxicity	0	0
Death	2 (40)	

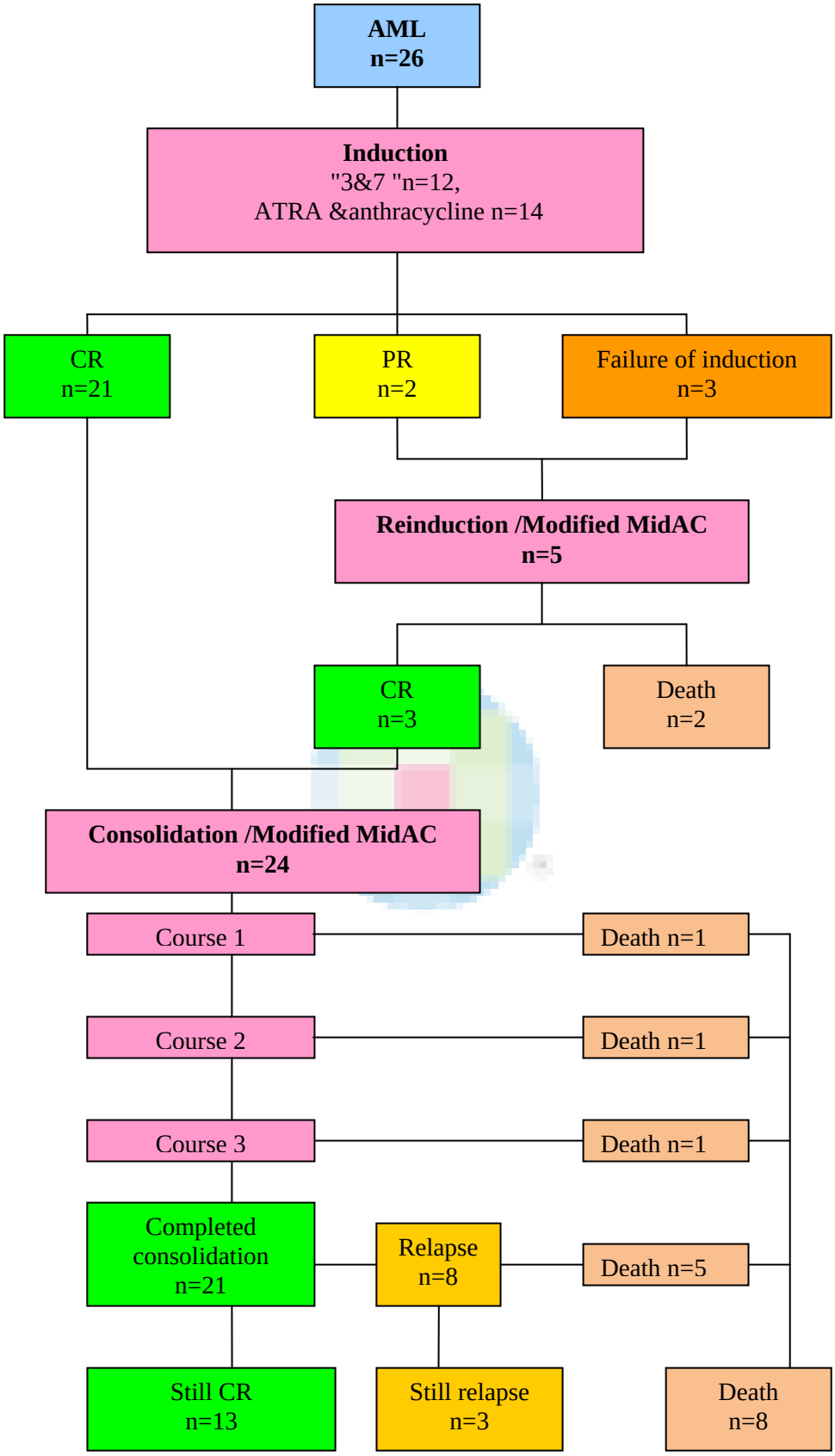

Figure 1: The study design

Results of induction therapy

Twenty six patients were given induction regimen with the standard 3&7 regimen or ATRA plus doxorubicin, according to the FAB subtype; 21 patients (80 %) had CR, 2 patients (8 %) had PR, and 3 patients (12 %)had failure of induction .

Those 5 patients who didn't have CR were given one course of modified MidAC as salvage therapy . Three of them entered CR, while the other 2 died because of sepsis Table **2.**

Toxicity of re-induction therapy

Anemia, fever, and GIT complications (diarrhea, Stomatitis, or nausea and vomiting) were the most frequent problems encountered .Sepsis and death occurred in 2(40 %) of patient .**(Table 3).**

Outcome of consolidation therapy

Three (12%) patients died during the period of consolidation; each one died shortly after taking the 1st, 2nd, and 3rd, course respectively .In all cases, the cause of death was sepsis .The rest 21(88%) patients completed the 3 courses of consolidation therapy .The total number of MidAC consolidation courses was 68 **.Table 4** shows the results of consolidation therapy .Sixteen patients (67 %) of the original 24 patients eligible for consolidation remained alive, with 13 patients (54 %) in continued remission till the end of the study(range from 3 to 27 +months.)The median duration of follow up is 11.7 months (range 3 to 27 + months).Median overall survival (OS)is 20 months and the 2 years OS is 41% **(figure2) .**

Median disease-free survival) DFS) is 17 months and the 2 years DFS is 37%) figure **3)**Median survival after relapse was 2.5 months) range 1 to 5 + months.)

Table 4: Outcome of consolidation therapy

	No.	%
Patient received consolidation	24	100
Still in Complete Remission (CR)	21	88
Death during consolidation	3	12
Relapse during follow up	8	38

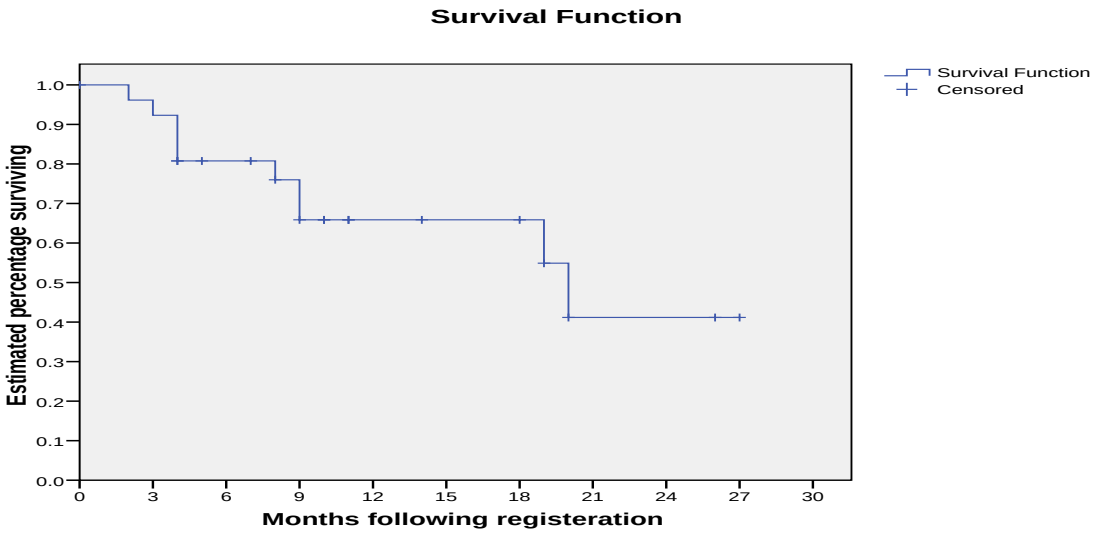

Figure 2: Kaplan-Meier overall survival (OS) of 26 patients showing median OS is 20 months and 2-years OS is 41%.

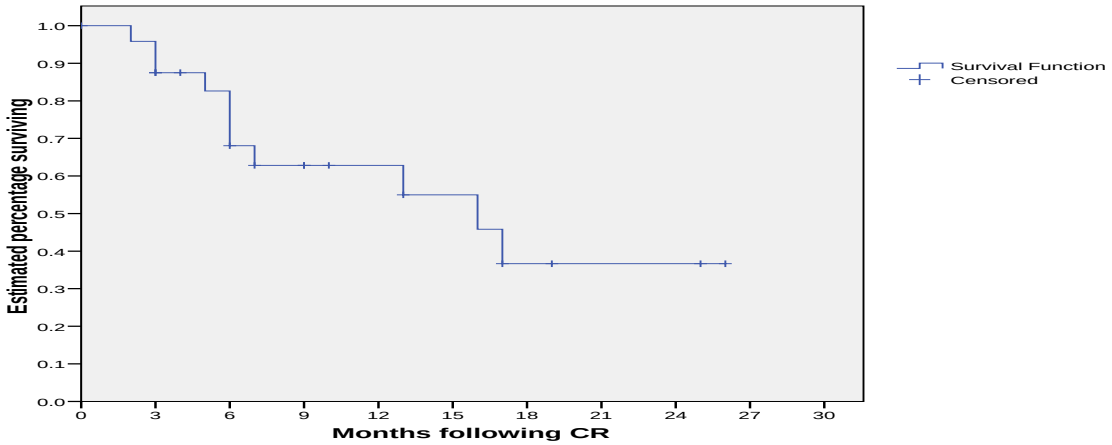

Figure 3.Kaplan-Meier disease-free survival (DFS) of 24 patients showing median DFS is 17 months and 2-year DFS is 37%.

Toxicity of consolidation therapy

Treatment related death occurred in 3 patients from the 24 eligible for consolidation .Death was due to sepsis in all the 3 patients. Serious neurotoxicity (cerebellar toxicity) occurred only in one patient. **(Table 5.)**

Table 5: Toxicity of modified MidAC regimen as consolidation therapy

	Grade 2 (%)	Grade 3 or 4 (%)
Anemia	30 (44)	9 (13)
Leucopenia	7 (10)	11 (16)
Thrombocytopenia	5 (7)	5 (7)
Bleeding	12 (18)	3 (4)
Fever	12 (18)	5 (7)
Nausea & vomiting	14 (21)	6 (9)
Stomatitis	17 (25)	4(6)
Diarrhea	3 (4)	2 (3)
Conjunctivitis	1 (1)	0
CNS toxicity	1 (1)	0
Death	3 (12)	

Discussion

After CR is achieved in AML, and in the absence of further treatment, virtually all patients will relapse, i.e. event free survival (EFS) will be zero .Moderate doses of consolidation chemotherapy significantly prolong the remission duration in randomized studies[12,13] The use of one to several courses of intensive consolidation chemotherapy may obviate the need for prolonged maintenance therapy .[14,15] Encouraging data have been reported using high dose cytarabine consolidation therapy [16] .

Another regimen recently suggested by the MRC AML15 trial is MidAC which is used in the intensification therapy for AML.[17]

In our study we tested the value of using modified doses of MidAC) mitoxantrone 2 instead of 5days and 8 instead of 10 mg/m^2)as a postremission consolidation therapy for AML patients .

We used this course of therapy as we can not supply the higher doses of Ara-C needed for HiDAC regimen for all our patients, along with the more toxic side effects that need more facilities which are not present in adequate standards in our hospital.

Although we don't have similar studies in Iraq using MidAC in consolidation of AML, many trials worldwide using HiDAC regimen as intensification is available (table 6).

Table (6).Comparison with trials evaluating HiDAC in intensification

Source	Post-remission regimen	CR (%)	Median age(yr)	Median follow-up (mo)	Median duration of CR (mo)	Complete responding continuous CR after 24 mo (%)	Toxic death (%)
Vaughan [18]	Ara-C, DNR	76	35	35	30	44	4
Preisler[5]	Ara-C, Dox, HiDAC	58	55	20	22	47	5
Wolff [16]	HiDAC, DNR	N/A	38	42	36	49	5
Harousseau[19]	HiDAC	76	44	60	43	40	12
Cassileth[12]	HiDAC/Amsa	68	44	48	N/A	28	12
Mayer [17]	HiDAC	64	43	37	N/A	44	5
BTH 2008	MidAC	80	25	12	10	53	12

N/A Not Available, BTH Baghdad Teaching Hospital (our study)

Median duration of remission was 10 months and this is inferior to that in other studies using HiDAC(30 month duration of remission) and this is possibly due to the shorter duration of follow up (11.7 vs .35 months)[18] .

Patients still in CR at the end of study were 13 (54%), this percentage appears to be higher than in other studies using HiDAC regimen and perhaps this is also due to small sample size, selection of young age groups and short duration of follow up .

Toxic death occurred in 12 %of patients receiving consolidation and this result is comparable to other studies using HiDAC regimen .There was no cardiac or hepatic toxicity, and only one case reported to have CNS toxicity .Incidence of infection was also equivalent with that in other studies .Thus, although the sample size was small and the duration of follow-up was short, we can add support to the plan of using MidAC regimen as a choice for patients with AML, either as salvage or as consolidation therapy[19] .

Modified MidAC regimen is an option as a consolidation or as a salvage therapy in the treatment of AML adult patients especially when high-dose Ara-C is not available .

Although sepsis is the major cause of mortality, it appears that there is no increase in the rate of major organ toxicity than when using other high-dose regimens .

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