

CYTARABIN AND DAUNORUBICIN OR IDARUBICIN IN INDUCTION THERAPY OF ACUTE MYELOID LEUKEMIA PATIENTS

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ABSTRACT

Objectives: Acute myeloid leukemia (AML), the most common form of acute leukemia, is treated by remission induction and post-remission therapy. Remission induction is usually achieved by administration of cytarabine along with an anthracycline such as Daunorubicin (DAU) or Idarubicin (IDA). Our objective was to see the benefits if any of IDA over DAU in AML therapy.

Methodology: Eighty adult AML patients were enrolled in this study, where 40 received DAU and 40 were treated with IDA. Remission status in each subject was studied and response to therapy was subsequently analyzed using SPSS.

Results: Complete remission, partial remission and no responsive status were 15, 19, and 14 respectively for patients on DAU and 14, 18, and 11 for patients on IDA protocol. No significant benefit was detected for IDA compared to DAU in response to therapy.

Conclusion: We found no benefit in using IDA over DAU in induction therapy for AML patients treated in northwest of Iran.

KEY WORDS:

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INTRODUCTION

Acute myeloid leukemia (AML) is known as the most common form of acute leukemia among adults with higher incidence in older patients.¹ Treatment of acute myelogenous leukemia (AML) is divided into remission induction and post-remission therapy. Remission induction is usually with cytarabine and an anthracycline.² Induction therapy for newly diagnosed AML patients should consist an administration of cytarabine (100 mg/m²) as continuous intravenous infusion over 24 hour for a week along with and daunorubicin, idarubicin, or mitoxantrone.³

As reported by Tallman MS⁴ and Bishop JE,⁵ approximately, 50 to 75 percent of adults with AML achieve complete remission (CR) when

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treated with cytarabine and any one of daunorubicin, idarubicin or anthracenedione mitoxantrone. Further reports have described a superior benefit for IDA,^{2,6,7} while other studies reported a higher remission rate.⁸ Our objective was to see if IDA has any benefit over DAU in AML therapy.

METHODOLOGY

We studied 80 adult patients diagnosed as AML and treated them in Shahid Ghazi Hematology Oncology Center from 2005-2008. Patients were diagnosed as AML after examining peripheral blood and bone marrow aspiration slides stained by Wright Giemsa, along with reports of cytochemistry, immunophenotyping and bone marrow biopsy tests. Criteria for AML diagnosis was detecting a minimum of 20% myeloblasts in the bone marrow aspiration while slides were reviewed by two hematologists. Bone marrow biopsies were reported by hematopathologist. Unfortunately, cytogenetics or molecular studies were not available.

Forty patients received cytarabine (100 mg/m²) over 24 hours infusion for seven days along with intravenous administration of DAU (45 mg/m²) for three days. The other group of patients were treated the same way but IDA (12 mg/m²) replaced DAU. Patients diagnosed with AML type M3 also received a 45 mg/m² dose of All-trans-Retinoic Acid (ATRA) in addition to chemotherapy. All patients gave informed consent. Antibiotics, granulocyte colony stimulating factor (GCSF) and packed cell or platelet transfusion were used based on our routine protocols. Inclusion criteria were all adult AML patients who were eligible to receive chemotherapy. Excluding criteria consisted ejection fraction of <45% in echocardiography or having ECOG 3. Four hematologists reviewed the

bone marrow aspiration for remission status 14 days after chemotherapy. Remission was established by 25% or more bone marrow cellularity, less than 5% of myeloblasts and improving peripheral blood and clinical status. To confirm complete remission, another bone marrow aspirate was examined a month later. Patients who had established remission according second aspiration received two courses of consolidation therapy but patients with partial remission (those with 5 to 20% blasts in bone marrow) received another course of the induction protocol. The non responsive cases, which were shown to have more than 20 percent of blasts in the bone marrow, were excluded from the study and treated with a salvage regimen. The data collected in this study were analyzed by means of SPSS.

RESULTS

Demographic status of the two groups of patients and the response to treatment as well as details regarding partial remission after repeated treatments are shown in Table-I, II and III respectively.

This study showed that complete remission, partial remission and nonresponsive status were 15, 19, and 14 for patients on DAU and 14, 18, 11 for patients on IDA protocol. Based on the probability value of equal to 0.977 & 0.918, no significant difference was seen between the two induction protocols in terms of response to therapy. No difference was also seen in response to therapy in different age groups.

DISCUSSION

Several reports have shown superiority of chemotherapy regimens containing IDA in the treatment of AML patients.^{6,7} Higher response rate or survivals in some age groups have been shown accordingly.⁸ This study was conducted

Table-I: Demographic status of two groups of patients is described below.

Groups	Sex		Age						
DAU	Male	Female	10-20	23-30	30-40	40-50	50-60	60-70	70-80
	23	17	5	12	9	6	5	1	2
Groups	Sex		Age						
DAU	Male	Female	10-20	23-30	30-40	40-50	50-60	60-70	70-80
	26	14	7	12	7	7	5	2	0

Table-II: Response to treatment as evaluated after examining slides prepared from bone marrow aspirates.

		First BM			
DAU	Unknown	Dead	C.Remission	P.Remission	No reponsive
	1	3	12	13	11
IDA	Unknown	Dead	C.Remission	P.Remission	No reponsive
	2	3	13	12	10

to evaluate response to therapy in adult AML patients on two different chemotherapy protocol containing Cytarabine plus DAU or IDA (7+3) in Tabriz, Iran.

The outcome of adult patients with AML depends on a variety of factors including age, intensity of post remission therapy, biologic characteristics of the disease and the most important is the status of relevant cytogenetics at presentation stage.⁴ We couldn't find any superiority using IDA in regard with the response to therapy. However, the survival of patients may show differences in respect with receiving DAU or IDA. This study did not include cytogenetic studies. The cytogenetic status of patients in different regions and makeup may also influence the response to chemotherapy. The age of the patients is another factor for evaluating the outcome, Kimby E. and coworkers reported a higher CR rate, especially in younger patients receiving IDA in induction therapy.⁸

AML in the elderly patients is characterized by intrinsic biological features implying an enhanced chemoresistance. Leoni F and colleagues evaluated the efficacy of an induction protocol with attenuated-dose of 8 mg/m² IDA for 3 days plus cytarabine and Etoposide in 26 AML patients aged above 60. The values of the area under the serum concentration curve of IDA metabolite indicated that the two patient groups received a very similar exposure to the drug despite the different doses.⁹

Table-III: Response to therapy in patients with partial remission after repeated treatment is described below.

DAU-Partial			
Unknown	Nonresponsive	C. Remission	Partial
1	3	3	6
IDA-Partial			
Unknown	Nonresponsive	C. Remission	Partial
4	1	1	6

We used the same dose of chemotherapy drugs in young and elderly patients and did not see any difference in response regarding the age. Nevertheless, the survival of patients could be evaluated in the other study.

Long term complications, cost effectiveness and toxicity of the therapeutic regimens are important matters in any chemotherapy protocol designation. Some reports denote less cardiotoxicity for IDA than other antracyclins.^{10,11} We had any clinical cardiac dysfunction in the two groups of patients but it needs long term follow up of the patients for adequate evaluation. IDA is expensive than DAU in our country (~1000 \$ Versus 360 \$ for 3+7 protocol) so IDA containing protocol would be ~ 1500 \$ more expensive than DAU containing regimen in the treatment of the patient (one 3+7 induction and two 2+5 consolidation protocol).

Gastrointestinal (GI) toxicities including mucositis, nausea and vomiting, and hepatic dysfunction are the most common reported side effects for IDA.^{12,13} We observed no clinical correlation in GI toxicities regarding IDA versus DAU.

The karyotype of the leukemia cells may provide three groups of favorable, intermediate, or poor at prognosis. Other factors include the presence of transmembrane transporter proteins, which extrude certain chemotherapy agents from the cell and confer multi drug resistance. Mutations in specific genes such as *WT1*, *CEBPA*, *BAX* or their over-expression and the ratio of *BCL2* to *BAX*, *BAALC*, *EV11*, *KIT*, and *FLT3* could alter the cytogenetic status of patients and their responsiveness to chemotherapy regimen.⁴

Lack of molecular and cytogenetic investigations in using IDA for treatment of AML in Iran potentially hinders a clear resolution for inter-

Table-IV: The results of statistical analysis of IDA and DAU below.

IDA				
	<i>Cumulative percent</i>	<i>Valid percent</i>	<i>Percent</i>	<i>Frequency</i>
Complete remission	32.5	32.5	32.5	13
Partial remission	62.5	30.0	30.0	12
Non-responsiveness	87.5	25.0	25.0	10
Dead	95.0	7.5	7.5	3
Non-reliable	100.0	5.0	5.0	2
Total	---	100.0	100.0	40
DAU				
	<i>Cumulative percent</i>	<i>Valid percent</i>	<i>Percent</i>	<i>Frequency</i>
Complete remission	30.0	30.0	30.0	12
Partial remission	62.5	32.5	32.5	13
Non-responsiveness	90.0	27.5	27.5	11
Dead	97.5	7.5	7.5	3
Non-reliable	100.0	2.5	2.5	1
Total	---	100.0	100.0	40
Chi-Square Tests				
Pearson Chi-Square	Asymp. Sig. (2-sided)		df	Value
Likelihood Ratio	0.977		4	0.461
Linear-by-Linear Association	0.977		4	0.467
N of Valid Cases	0.918		1	0.011
Pearson Chi-Square	---		---	80

pretation clinical data. Better definition of the complex process initiating and sustaining the leukemia process will lead to a better therapeutic intervention and improved cure rates. Specific attention must be given to prognostic factors that identify subtypes of AML in which specific tailored therapies may provide superior efficacy.

CONCLUSION

This study demonstrated no benefit of IDA over DAU in induction therapy for AML patients in northwest of Iran. Further studies are needed to assess survival rate of the patients in correlation with response to therapy with including prognostic factors.

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