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EFFECT OF LONG- AND SHORT-TERM MINICONSOLIDATION ON SURVIVAL OF PATIENTS WITH ACUTE MYELOGENOUS LEUKEMIA

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ABSTRACT

A retrospective study was done on 130 AML patients treated in Shariati and Imam Hospitals in Tehran from 1991 to 1997 to investigate the value of three post-remission methods of treatment.

All patients who were in complete remission (CR) (Group I) had been treated with ARA-C (300 mg/m^2/day continuous infusion for 5 days) and Daunorubicine (45 mg/m^2/day for 3 days) as induction and early consolidation therapy. Forty patients were treated by additional similar chemotherapy as second consolidation and no further treatment was offered. Fifty patients (Group II) were treated by ARA-C (120 mg/m^2 subcutaneously for 5 days), Etoposide (120 mg/m^2 on day one), and Mitoxantrone (12 mg/m^2 on day one) on each successive month as short-term miniconsolidation. Forty patients (Group III) were treated similarly to Group II until relapse for up to two years as long-term miniconsolidation.

There was no difference in the three groups regarding mean age and other prognostic factors. Treatment related mortality and morbidity were also similar. Median duration of disease-free survival (DFS) was 36 (3.5-68 with 95% CI), 17 (12.5-21.5) and 19 (14.7-23.3) months respectively in these three groups. In a 14-month median observation there was no difference in DFS and overall survival (OS) among the three groups (p=0.7).

We concluded that short- or long-term miniconsolidation chemotherapy compared to standard treatment does not improve DFS and OS in AML patients.

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INTRODUCTION

Remission induction (RI) with ARA-C and Anthracyclines is standard treatment in AML, but post-remission treatment differs widely. Standard RI causes CR in 70% of AML patients, but with no further treatment, long-term event-free survival is nearly impossible[11,20,27] Post-remission treatments tend to eradicate detectable residual leukemic cells with molecular biology methods.[5] Several attempts have been made to improve

treatment results by altering the duration or kinds of drugs used in the remission induction phase, but few or no benefits have been achieved [12,16] Over the past 30 years there have generally been three classic ways of AML treatment in the post RI period:

1. Maintenance therapy: This prolonged low-dose chemotherapy treatment has been used to increase the DFS or OS.[14,17,18]

2. Consolidation therapy: In this way two or more courses of combination chemotherapy, comparable with RI in intensity, have been offered to patients.[5,7,26]

3. Intensification therapy: Newer attempts with more attractive results have been obtained mainly by more intensive chemotherapy post RI to eradicate the residue of leukemic cells in the bone marrow.[6] It seems that more intensive treatment in the post-remission period causes a more prolonged duration of DFS; but intensive chemotherapy usually results in more morbidity and mortality due to drug toxicity.[1,6,25]

In this study we present the treatment results of higher doses used in conventional maintenance chemotherapy for variable duration after RI and compare this treatment with two courses of consolidation therapy. As the drug doses used in these treatments are more than conventional maintenance therapy but less than classic consolidation therapy, we called this treatment miniconsolidation."

PATIENTS AND METHODS

In a retrospective study all AML patients treated from 1990 to 1997 in Shariati and Imam Hospitals in Tehran were considered. Both medical centers are affiliated with Tehran University of Medical Sciences. The criteria were:

1. Patients whose peripheral and bone marrow studies, reported by a pathologist and hematologist, favored AML according to FAB classification.

2. Patients under 60 years of age.

3. Patients who had not previously received chemotherapy.

4. Patients who had received ARA-C (300 mg/m^2/d continuous infusion for 5 days) and Daunorubicine (45 mg/m^2 for the first 3 days) as induction, and classic criteria of remission have been satisfied by one or two courses of the above-mentioned treatment.

5. Patients with preceding myelodysplasia were excluded.

Complete remission was defined as the presence of normal bone marrow with less than 5% blasts, at least 1,500 granulocytes per cubic millimeter, and 100,000 platelets per cubic millimeter in the peripheral blood.

Therapeutic failure causes were subdivided into three categories: resistant leukemia, death during treatment-induced bone marrow hypoplasia, and death within ten days following remission induction therapy. All of these cases were omitted from this report.

In this study DFS was measured as the length of time from complete remission criteria satisfaction to relapse or death from any cause other than relapse.

Patients who achieved CR had been treated in three fashions as post-remission treatment.

1. Patients treated in Shariati Hospital received two courses of consolidation chemotherapy of the same dose. This treatment was considered as standard treatment.

2. Some patients had been treated by ARA-C (120 mg/m^2 subcutaneously for 5 days) and Etoposide (120 mg/m^2 on day one) with or without Mitoxantrone (12 mg/m^2 on day one) on each of six successive months after remission induction, and a single course of consolidation therapy with a similar regimen as remission induction. This group was called the short-term miniconsolidation group.

3. The third group was treated by the same regimen as Group II, until relapse or for a maximum of 2 years, as long-term miniconsolidation therapy.

The number of patients evaluated totaled 1,083. There were 40, 50 and 40 patients eligible according to the above-mentioned criteria in each successive group respectively. Adding Mitoxantrone in each course of treatment in Groups II and III depended on the patient's CBC and was included when WBC exceeded 4000/mm^3.

Remission induction and two courses of consolidation were given as in-patient treatment to patients in Group I. Patients in Groups II and III received remission induction and a single course of consolidation.

Patients in Group I were followed monthly without further treatment. This follow up included physical examination and peripheral blood smear checks every month. And in cases of suspicious relapse immediate bone marrow exam was carried out. OS and DFS distribution were estimated by the Kaplan-Meier method and tested for equality by log rank test. Risk factor frequencies in each group were compared by Chi-square test. The mean age, duration of admission, and expenses were compared by t-test in these groups.

RESULTS

Patients' characteristics are summarized in Table I. It is evident in Table I that there is no significant difference regarding age, subtypes of AML and remission induction times as prognostic factors in these groups.

Median duration of follow up was 14 months. Median duration of DFS in patients who were under or over 40 years of age were 19 (2.1-35.9, 95% CI) and 21 (13.9-28.1, 95% CI) respectively, which was statistically insignificant (p= 0.13).

Median duration of DFS in Groups I, II and III were

Table I. Characteristics and prognostic factors in 130 AML patients treated in three post-remission chemotherapy sessions.

Group	Age			Sex		Remission induction time		Subtype		Total
	Mean	Max	Min	Male	Female	One	Two	M1, M2, M3	M4, M5 M6	
Group I	28.9	56	14	20	20	56	4	15	25	40
Group II	29.7	65	12	26	24	41	9	26	24	50
Group III	34	72	13	20	20	35	2	22	18	40
p value	0.3					0.18		0.21		

36 (3.5-68.5, 95% CI), 17 (12.5-21.5, 95% CI) and 19 (14.7-23.3, 95% CI) months respectively, with insignificant difference (p= 0.7). A comparison of DFS and OS in these groups is summarized in Table II.

As it is evident, there is no statistical difference between DFS and OS in these three groups. The probability of remaining disease-free in relation to the type of post-remission therapy was insignificantly different in 98 patients under the age of 40 and the 32 patients who were over 40 years of age; so these two groups were combined for further analysis. Among 130 patients, the likelihood of remaining disease-free after 18 months was 40% in the first group, 31% in the second group, and 39% in the third group with p= 0.4 (Fig. 1).

The main causes of hospitalization in order of frequency were fever, neutropenia and sepsis in 218 cases, and continuous infusion of drugs in 173 cases.

There was no treatment-related mortality in these three groups, but treatment-related side effects, including hematological toxicities, cardiac toxicities, etc., occurred in all three groups which are summarized in Table III.

Mean cost of drugs used were 169,200 Rials (Rls), 486,750 Rls and 1,292,930 Rls respectively, which was significantly higher in Groups II and III (p= 0.008 and p= 0.0001). Patients in Groups II and III received more prolonged treatment; therefore all costs, including direct treatment costs, direct non-treatment costs, and indirect costs, were more in these groups. Direct treatment costs are those for items used by the health sector to provide treatment. Direct non-treatment costs are those for resoures used by patients and family to gain access to and participate in treatment such as travel, parking and accomodations near a cancer treatment center. Indirect costs are expenses for lost work time incurred by the patient and family required for treatment. A total of 673 courses of miniconsolidation therapy were administered; hospitalization because of fever and neutropenia was required in 30.5% of courses; and packed cell and platelet transfusions were needed in 31.5% of cases.

Table II. Patient outcome with three post-remission therapy sessions.

Group	9-Month disease-free survival	18-Month disease-free survival
Group I	0.61	0.45
Group II	0.64	0.32
Group III	0.75	0.41
p value	0.7	0.4

Table III. Hospital stay and toxic effects following post-remission chemotherapy in three groups.

Group	No. of patients	Treatment courses analyzed	Treatment courses requiring hospitalization	Mean number of hospitalization days per person	Treatment courses requiring blood product transfusion	Cardiotoxicity
Group I	40	80	80 (100%)	28	64	3
Group II	50	345	143 (41%)	29	96	4
Group III	40	418	168 (100%)	38	118	4

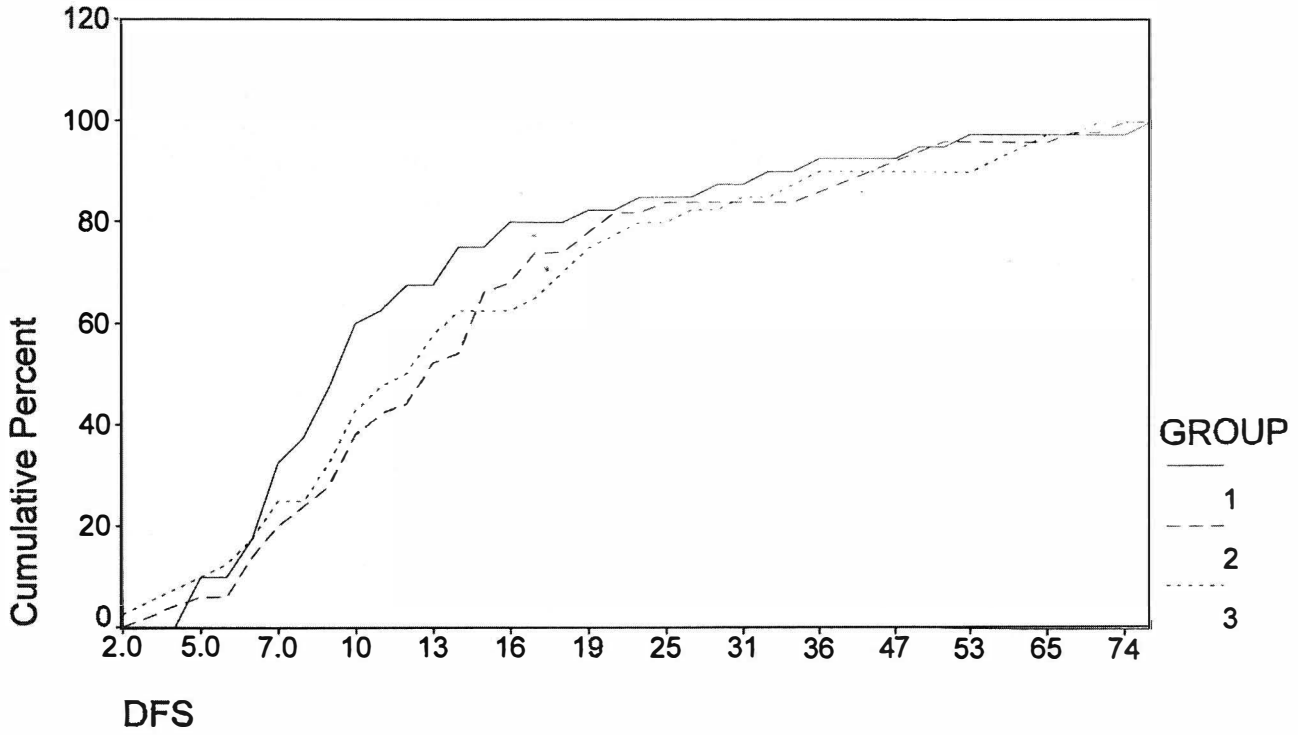

Fig. 1. Cumulative survival curve.

DISCUSSION

Until the early 1980s most AML treatment protocols consisted of one or two bone marrow aplasia inducing treatment cycles followed, if remission was achieved, by monthly maintenance out-patient treatment designed so as not to induce bone marrow aplasia.[4,10] Median survival time of patients going into remission (53%) was a little over one year.[2,3,7] The fact that maintenance regimens which did not induce marrow aplasia left sufficient tumor cells when there was minimal residual disease caused doubt about the effectiveness of this treatment.[23]

We hereby present two kinds of post-remission treatments which cause moderate bone marrow aplasia and are more aggressive than conventional maintenance and less toxic than consolidation therapies, using high dose or intermediate doses of ARA-C. The difference between these two is the duration of therapy. The finding of insignificant difference between these two forms of miniconsolidation therapy confirm that a longer duration of treatment does not prolong the duration of remission. Although miniconsolidation is continued for a long time (maximum 2 years in this study), the great majority of its effectiveness is probably derived from the early months of treatment after complete remission. This can be seen in the survival curve (Fig. 1) that shows a crossing of survival curves in the first months of treatment with slight superiority of Groups II and III. But it is evident that in longer follow-up there is no difference in the survival rate between Group I, II and III. Median duration of DFS shows a more prolonged time in Group I compared with Groups II and III. Although this difference is statistically insignificant, it may be a clue to the existing significant difference in larger series of patients in future follow-up. In a CALGB study, in which patients in complete remission were randomized to 8 months or 3 years of maintenance therapy, there was no difference in long-term event-free survival.

Similarly, when repeated courses of induction therapy were administered over 3 to 5 months after CR, before randomization to maintenance therapy or observation, maintenance therapy confered no additional benefit.[5]

In a previous trial the ECOG randomized patients to receive or not receive two reduced dose courses (by approximately 1/3) of induction therapy before commencing the maintenance program with a 2-year median duration of follow up. EFS for this miniconsolidation plus maintenance versus maintenance therapy alone was 28% versus 14% at 3 years. An update of the data with a median follow up duration of 8 years shows an EFS of 24% versus 12% due to late relapses, suggesting that this only moderately intensive post-remission therapy may have

an improved long-term outcome.[5]

This study again confirms the role of intensity of post-remission therapy in improving the survival.

Several studies[1,6] showed the efficacy of high dose Cytosar in post-remission treatment of AML. Several studies also showed the ineffectiveness of using high dose ARA-C or other drugs as part of the RI regimen in remission rate and the rate of OS. So the remission induction regimen has not changed over the past 30 years. We used a moderately myelosuppressive regimen in arm 2 and 3 in our study and we found no difference in survival rate between these two arms. Regarding several studies that showed the benefit of high doses of ARA-C in the post-remission period and our study results, we can conclude that:

1. The most important factor influencing the duration of DFS and overall survival in AML patients is the intensity of post-remission treatment.

2. More prolonged treatment with moderate myelosuppressive effects does not increase the DFS and OS. As these treatments are not cost-effective and have comparable toxicity with short courses of more intensive therapy, we do not recommend using these treatments.

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