Out-Patient Consolidation Therapy in Patients with AML by Mitoxantrone, Etoposide and Cytarabine

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Abstract

History and Goals: Now a days, the main purpose of treatment in patients with Acute Myeloid Leukemia (AML), is achieving a "definite cure", and this goal is impossible unless stem cell transplantation (bone marrow transplantation) or the administration of high-dose Cytarabine is performed.

As these therapies are very expensive and money consuming, and due to restricted application of these procedures in Iran, most hematological clinics in Iran, prefer to have a classical approach in such instances.

These approaches consist of 4 cycle performing a 4 months period of hospitalization.

In patients who can not pay the cost of treatment and have a low socioeconomic and cultural status, maintaining therapy is very difficult and usually unsuccessful.

Out patient consolidation therapy is an alternative to cope with such problems.

Material and Methods: As a clinical trial, all cases of AML, admitted to Taleghani Hospital (Kermanshah–Iran) from December, 1998, after achieving complete remission and receiving first consolidation therapy were selected to be evaluated.

For patients who could not accept long time hospitalization because of their socioeconomic, financial status, consolidation therapy was arranged for them as outpatients, for 6 continuous cycles, every 3-4 weeks.

Other patients received 2 runs of classic consolidation therapy in hospital.

Findings: Till October 2002, of the 57 patients admitted with AML diagnosis, 7 cases were excluded because of advanced age (age>65) and functional weakness and 3 patients died as a result of early complications. Of the 47 remaining patients, 39 cases achieved complete remission with induction therapy. 23 of the treated patients received out-patient consolidation therapy and 16 cases underwent classical therapy.

During the follow-up period which lasted between 7 to 47 months, in the classical therapy group, 8 cases of relapse occurred leading to the death of 5 patients, whereas in the out-patient group, 12 relapses occurred in which 7 persons died.

From an overall survival (OS) and disease free survival (DFS) point of view, no notable and meaningful difference was seen. But, complications of therapy necessitated blood product administration and increased amount of hospitalization, which was significantly more frequent in patients assigned to classical therapy compared to the out-patient group.

Discussion: According to the results of this study and a few identical studies performed previously in Imam Khomeini and Dr Shariati Hospitals (Tehran-Iran), although, out-patient consolidation therapy takes more time, but, because of shortened hospitalization time, ease of performance and tolerance by patients, this therapy can be applied to all patients with a low socioeconomic status. Moreover, from an ethical point of view, physicians can be assured that there is no difference in relapse and mortality rate compared with the classical approaches.

Obviously, this therapeutic approach can be generalized and extended to other regions of Iran, and in underdeveloped countries with the same limitations and problems.

Keywords: AML, Consolidation therapy, Etoposide, Cytarabine

Backgrounds and Objectives

Acute Myeloid Leukemia (AML) is a kind of blood cancer characterized by proliferation and aggregation of myeloid blasts in bone marrow and consequently, the involvement of blood and other organs.

In the United states, it's crude incidence is 2.25 cases/100000 of total per year.

Curative treatment of AML is stem cell transplantation (bone marrow transplantation). Shortly after the first remission, is the best time for performing transplantation.(1-4)

If there is no possibility of applying bone marrow transplantation, the patient should receive 3 cycles of consolidation therapy with high-dose Cytarabine, or other combined therapeutic regimens containing low to moderate doses of Cytarabine, all after induction remission.(1-6)

A 5 year overall survival rate of patients undergoing intensive chemotherapy with high-dose Cytarabine is about 30%, and for transplanted patients it is about 50%.(1-4, 7, 8)

Multiple studies have been performed to compare these 2 approaches: intense chemotherapy with high-dose Cytarabine and bone marrow transplantation. In most of them no significant differences in overall survival and disease free survival have been reported.(2, 3, 6)

At present, in Iran, bone marrow transplantation is applied in just two centers:

Dr Shariati Hospital in Tehran and the **Namazi Hospital** in Shiraz.

Since March 1991, about 137 cases of AML in Tehran, and about 42 cases in Shiraz have been transplanted. This means that bone marrow transplantation is a restricted procedure and is not being performed widely (just 16 cases of AML per year). On the other hand, it must be noted that only 1% of patients with AML undergo transplantation.[9, 10]

Consolidation therapy with high-dose Cytarabine needs centers which can provide an adequate infrastructure including a full isolation service. Unfortunately, only a few centers in Iran have such characteristics.

According to Dr Keyhani's study (Dr Keyhani et al.) performed at the Imam Khomeini Hospital (Tehran– Iran), a therapeutic regimen containing low doses of Cytarabine (given 100mg/m^2/7days) combined with Daunorubicine, given once as an induction remission and given 3 more times, as consolidation therapy, is the best procedure for patients with AML in Iran.[11]

Apart from this study, since 1991, in the Imam Khomeini Hospital (Tehran-Iran), out-patient consolidation therapy with Cytarabine, Mithoxanterone and Etoposide has been performed on many cases of AML.[12, 13] An important problem in the treatment of AML patients, in Kermanshah and certain regions of Iran, even in Tehran, is the inability and low tolerance of some patients to accommodate 4 hospitalizations in a 4 month period, because of their socioeconomic and cultural poverty. This obliges them to give up the treatment process and leave it uncomplete.

Out-patient consolidation therapy with Cytarabine, Mithoxanterone and Etoposide can help to reduce the aforementioned problems.

Material and methods

A clinical trial was planned for AML patients. The diagnosis of AML was made upon morphologic assessment of bone marrow aspirated samples, and in some instances, by means of flowcytometery.

All diagnosed patients were admitted to take induction remission, given continuous intravenous infusion of 100mg/m^2 Cytarabine for 7 days and direct intravenous infusion of 45 mg/m2 BSA of Daunorubicine for 3 days, once every day.

Patients who entered the remission phase, also received the first run of consolidation therapy in the hospital, as performed for induction remission.

In the next step, patients were divided in to two groups:

Those who could not to continue therapy in the hospital, who were then selected for out-patient consolidation therapy (in an out-patient consolidation therapy group) and the rest of the cases, which received a third cycle of consolidation therapy as did in-patients (classical consolidation therapy group).

The only criteria in categorizing patients in each group, was their own inclination, so this trial was not a randomized study.

Patients of the out-patient group were given 200 mg subcutaneous Cytarabine for 5 consecutive days and 12mg/m2 Mithoxanterone and 120 mg/m2 intravenous Etoposide on the first day of treatment. This protocol was repeated each 3-4 weeks, up to 6 successive cycles.

CBC was checked in all outpatient cases, one day before starting the protocol and rechecked on the 5th day. If CBC was under 3,000 cell/µl or platelet count became less than 100,000/µl, the therapy was discontinued.

When hemoglobin levels dropped below 8g/dL and the platelet count was under 20,000/µl, blood transfusion was performing.

All patients were instructed through the use of brochures and pamphlets and warned about complications of treatment, especially about infectious complications and preventive measures. All patients of the classical therapy group were under close observation, as well.

After finishing the treatment process, all patients were followed up and visited monthly, and their CBC was checked. In patients suspected of relapsing, bone marrow aspiration was assessed.

Patients who became refractory to induction remission or those who encountered relapse, were all excluded.

In all, of the 57 cases admitted to the Taleghani Hospital, 7 patients who were older than 65 and 3 patients who died before the beginning of any therapy, due to complications of their disease, were excluded.

Of the remaining patients, 8 cases became refractory to treatment and were excluded, too. 39 instances responded, 23 of them received out-patient consolidation therapy and 16 cases went under classical therapy.
Data obtained from these two groups, were analyzed by means of the odds-ratio and Fischer's accurate tests and compared to each other.

Findings

The studied patients were between the ages of 13-65, with an average age of 33 years.
47.8% of the patients were female and 52.2% of them were male.
From a socioeconomic status point of view, 90% of cases in the out-patient group were set in the low to intermediate classes. Also, in the classical therapy group, 90 % were unemployed but fell into the intermediate socioeconomic class.
The minimum time of follow-up was 7 months and the maximum time was 47 months.
The most frequent subtype of AML was AML-M4 and the least common subtype was AML-M6 (Table 1).

Table 1: frequency percentage of AML subtypes among all patients.

Sub type	No	Percent
M0	0	0
M1	5	8.5
M2	18	31.6
M3	6	10.5
M4	17	29.8
M5	9	15.8
M6	2	3.5
M7	0	0
Sum	57	100

Some patients of the classical group, in addition to hospitalization for each cycle of consolidation therapy, were admitted again (on the average, 6 times) due to complications such as neutropenia, hemorrhage and abscess formation. These patients received, on average, 8 units of blood and 40 units of platelets.
In contrast, the average amount of blood products during transfusions for the out-patient group was 4 units of blood and 24 units of platelets.
Eight patients of the classical group encountered relapse, leading to death in 5 instances (31.25%).
In contrast, 12 cases of the out-patient group encountered relapse. Among them, 7 patients have died till now.
In all, there were no meaningful statistic differences in mortality rates and the number of relapses, between these 2 groups (Table 2, 3). Overall survival (OS) and disease free survival (DFS) in both groups were equal and no differences were seen (Table 4).

Table 2: Mortality rate among both groups of patients with AML

Sum		Achievement method					
		classic		outpatient			
%	No.	%	No.	%	No.		
30.8	12	31.25	5	30.4	7	**Yes**	***Death***
69.2	27	68.75	11	69.6	16	**No**	
100	*39*	*41*	*16*	*59*	*23*	***Sum***	

Table 3: relapse rate among both groups of patients with AML

sum		classic		outpatient			
%	No	%	No	%	No		
48.7	19	50	8	47.8	11	**Yes**	***Death***
51.3	20	50	8	52.2	12	**No**	
100	*39*	*41*	*16*	*59*	*23*	***Sum***	

Table 4: OS and DFS rate in both groups of patients with AML

P-Value	Type of achievement		
	Outpatient	Classic	
NS	22.6±10.9	23.1±12.1	**OS (month)**
NS	19.1±9.7	20.4±10.3	**DFS (month)**

Discussion

There were no notable statistical differences in overall survival (OS) and disease free survival (DFS) of both groups. But the number of hospitalization and the amounts of blood products transfusion in patients of the classical group were higher than the other group.
The main purpose of our study was designing and performing treatment for patients with AML; not only to shorten the duration of hospitalization, but also to lower the cost of treatment and decrease the stress of being in the hospital atmosphere.
These aforementioned problems, can disturb the progression of treatment in those with acute leukemia. Such difficulties can affect treatment even in other malignancies.
Due to the limited possibility of performing bone marrow transplantation and the routine administration of high-dose Cytarabine in Iran, we are obliged to apply the classical methods to achieve remission in most patients affected by AML.
In outpatient consolidation therapy, although patients received lower doses of medication, but decreasing of intervals of administration can overcome this defect.

There are no differences between the results of treatment with outpatient consolidation therapy, compared to the classical method. Moreover, physicians have no ethical limitation when using this method. Also, outpatient consolidation therapy has fewer complications in contrast to the classical method.

Outpatient consolidation therapy has been previously used in Iran. Since 1991 in Imam Khomeini hospital of Tehran Medical University, out-patient consolidation therapy has been performed in some patients with AML and the results of such work has been presented and published in some articles. According to a survey taken between 1991 and 1998, of the 130 patients with AML, 40 patients received outpatient consolidation therapy (our studied cases). Fifty of them received this therapy for 2 years, and the rest underwent treatment. At the end of this study, no differences in overall survival (OS) and disease free survival (DFS) were observed.[11,12]

Dr. Vaez, et al; in Tabriz tried medications in doses lower than amounts which we started for our patients.[14]

To establish a well-accepted method of consolidation therapy for patients who were unable to be hospitalized, Dr Vaez and his colleagues, applied only 40 mg of subcutaneous Cytarabine, daily, for 8 to 20 days: among the 19 patients, 8 cases had not received any therapy till that time, and 11 patients responded fairly to their method of treatment.

There is no discussion about the protocol that they used, a regimen combined with Mithoxanterone, Etoposide and Cytarabine. These medications have been well studied and applied in patients with AML.[15-18]

Administration of Cytarabine in doses lower than doses we administrated, especially in elderly patients, has been previously studied [19-22] in Iran by Dr Keyhani and his colleagues in Imam Khomeini Hospital of Tehran Medical University.[11]

Although in most hematological references the standard treatment features of therapy in AML by means of bone marrow transplantation and chemotherapy has been well defined, studies performed in under-developed countries applied customized protocols suitable for their cultural and socioeconomic status. The results of such studies have been published.

Al-BAhar and his colleague in Kuwait, Liang et al in Hong Kong, and Keshkin et al in Turkey all performed studies by means of new methods and the administration of adjusted doses of Mithoxanterone and Cytarabine, which were evaluated.[23,25]

It is obvious that the same method cannot be applied in all countries. Moreover, the cultural and financial status of patients are points that have to be noted in the treatment process. Our study is a step toward finding a way to treat patients who live in financial and cultural poverty.

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