TIME SEQUENTIAL HIGH DOSE OF CYTARABINE IN ACUTE MYELOCYTIC LEUKEMIA

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Abstract- Given preliminary evidence of timed, sequential chemotherapy of high dose cytosine arabinoside the current study was initiated to assess the side effects and efficacy of this regimen in patients with newly acute myelocytic leukemia(AML). Nineteen adults who referred to Hematology-Oncology and Bone Marrow Transplantation (BMT) research center of Tehran University of Medical Sciences were enrolled in a trial from Aug 1999 to Nov 2000. All patients had a Karnofski classification above 60%. At this time induction therapy consisted of daunorubicin or idarubicin given at a dose of 60 mg/m² and 12 mg/m² IV respectively on days 1-3, and cytarabine (Ara-C) 100 mg/m² intravenously by continuous infusion on days 1-7, followed by Ara-C 1000 mg/m² given on day 8-10 every 12 hours by IV infusion. Consolidation therapy started after 35th day. Of 19 fully evaluable patients, 10 patients achieved a complete remission, whereas 36.6% patients succumbed to death due to regeneration failure. The clinical data show that the overall survival rate from diagnosis is 55.5% (95% CI, 30.8-78.5) at 6 months for the entire cohort of the patients. Disease free survival is also 50% (95%CI, 26-74). Mean duration of death due to treatment was 20 days (range 17-29) after beginning the regimen. Presenting WBC counts, French-American-British (FAB) classification, sex and age were not useful prognostic variables. Fever, diarrhea, nausea and vomiting and GI hemorrhage were seen in 19, 6, 4, 7 patients respectively. It seems the 3+7+3 regimen is a promising approach for the AML patients regarding to high complete remission rate, but more supportive care should be considered. Furthermore any, benefit in long-term outcome can’t be determined regardless to the choice of post remission therapy (e.g., GCSF, appropriate antibiotics and etc).


Key Words: Leukemia myelocytic acute, antineoplastic protocols, high dose cytarabine

INTRODUCTION

It took long more than two decades after the introduction of cytarabine and daunorubicin, which was an important advance in the treatment of acute myelocytic leukemia(AML). In spite of improvement in supportive measures and this great advance, however, long-term survival for patients with AML has not raised beyond 40% yet. At present, the standard therapy for AML is the regimen of 3+7. More than 40% of patients treated with this regimen require a second course of chemotherapy because leukemic cells are still observed in the marrow on day 14. This additional cycle of therapy may increase complete remission rate and also decrease the frequency of relapse. There are several other methods to achieve this goal, which might be called as post remission therapy. It aims at eradication of the disease, and involves additional cycles of chemotherapy or bone marrow transplantation, or a combination of both. Time sequential chemotherapy (TSC) is one of the new methods and was designed to maximize the number of leukemic cells killed by cytotoxic agents by recruiting cells in the cell cycle using a first sequence of chemotherapy and then administering the second sequence using cycle-drugs, at the time of peak cell recruitment induced by the first sequence (1). On the other hand it is believed that with the high doses of cytarabine, the leukemic cells resistance can be overcome since it probably enters cells by passive transfer, thus resulting in higher intracellular levels. In 1987 a multicenter trial was designed and performed by Mitus and his colleagues (2). They modified the standard 3+7 chemotherapy program to 3+7+3 (high-dose cytarabine was added on day 8 through 10) in order to increase the remission rate and prolong survival in AML patients. Regarding the remarkable outcome of this trial and based on principles of time sequential therapy originally proposed by Preisler et al. (3,4), browman et al. (5), Vaughan et al. (6,7) and Burke et al. (8), in 1999 we initiated a trial to assess this regimen not only for its affect on remission and overall survival of AML patients, but also in

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determining some hidden conditions, like socioenomic
status of patients and the hospital facilities which are not
mentioned in detail in such studies. We modified the
3+7+3 regimen of Mitus trial after considering principles
of preliminary studies by others (1-12), and tried to
crystallize all the aspects of this regimen on AML
patients.

MATERIALS AND METHODS

Patient characteristics

Patients less than 55 years old with newly AML who
referred to Hematology-Oncology and BMT research
center of Tehran University of Medical Sciences were
enrolled in a trial from August 1999 to November 2000.
Patients with known antecedent myelodysplasia, or
documented unexplained anemia or other cytopenia were
excluded. Before starting therapy, all patients had
adequate hepatorenal function (Cr. <2.0 mg/dl, Bil. <2
mg/dl), cardiopulmonary function (normal PLFT,
EF>65%) and also their Karnofski classification grade
was above 60%.

French-American-British (FAB) classification was
performed according to standard morphologic and
histochemical criteria. Cytogenetic analysis and immu-
nophenotyping was obtained at diagnosis compatible
with the protocol. Complete remission (CR) was defined
as less than 5% myeloblasts in the marrow with
restoration of normal hematopoiesis of at least one
month duration. Toxicity grading was performed
according to CTC criteria (13). Induction and consoli-
dation therapy: Induction chemotherapy consisted of
daunorubicin 60 mg/m² or idarubicin 12 mg/m²
administered intra-venously on days 1 to 3 and
cytarabine 100 mg/m² administered by continuous
intravenous infusion (CIV) on days 1 to 7 followed by
high dose of cytarabine 1 g/m² infused over 75 to 90
minutes every 12h on days 8 to 10 (Fig. 1). Bone
marrow aspiration and biopsy were scheduled to be
performed on day 17 and at the time of peripheral blood
count recovery (absolute neutrophil count > 1500/µL).
All patients who achieved a CR received one course of
consolidation chemotherapy after day +35 as follows:
Daunorubicin 60 mg/m² or Idarubicin 12 mg/m² IV on
days 1 and 2 and cytarabine 100 mg/m² by CIV on days
1 to 5 followed by high dose of cytarabine 1 g/m² on
days 6 and 7.

At the time of enrolment in the trial all patients got
insight to the protocol by their own physician
individually and signed the consent form. In case they
had no tendency to enter this trial we started the standard
regimen. During treatment the mortality and morbidity
data were analyzed biweekly. Therefore if

any irrational results appeared therapy would be
interrupted.

Statistics

The outcomes measured in this study were proportion
of patients entering complete remission, overall survival,
disease-free survival (DFS), relapse rate and treatment
related toxicity. Overall survival, DFS, and probability
of relapse were analyzed according to the method of
Kaplan and Meier and 95% confidence interval were
calculated with Greenwood's formula. DFS was defined
as time from diagnosis to relapse or death from any
cause. A stepwise multiple logistic regression analysis
was performed to determine if previously reported risk
factors were related to remission rate and survival.
Variables used in this analysis included as the following:
Age, FAB classification, cytogenetics, tumor infiltration,
organo-megalgy and presenting WBC count qualitative
variables were compared with pearson X² analysis at a.
<5% in all tests. Data were analyzed from November 20,
2000, which yielded a median follow up time of
surviving patients of 180 days.

RESULTS

Nineteen patients with de novo AML were enrolled
on to the study; there were 10 females and 9 males. The
mean age of the cohort was 30.3 years, and ranged 15-45
years. Patients' characteristics are listed in table 1. They
were compared with the data of Mitus survey and
marked if any significant difference appeared. The
complete remission rate was 52.6% among 19 cohort
patients. Death due to regeneration failure occurred in
6/19 (31.6%) of patients and most of them were the
result of neutropenia and secondary sepsis. Sepsis was
the cause of death in 83.3%, there was only one death
due to sepsis occurring after the patient had achieved a
CR. One additional patient was excluded from this case
series before the day 35 because of intolerance to
therapy. Two patients never achieved remission. One of
them despite two additional courses died after 14 months
of initiating therapy. The other did not tolerate treatment
after day 35. There were no significant differences in
mean age (P=0.4) and presenting WBC count (P=0.2)
between the Mitus and this study. In those patients who
achieved a CR, the median time from initiation of
therapy to platelet Count recovery (untransfused platelet
count >20,000/µL) was 6.5 days (range, 2-11) and the
median time to neutrophil recovery (absolute neutrophil
count >500/µL) was 14.4 days (range, 7-21). All patients
who developed fever were treated with broad
spectrum antibiotics. The
median time for the duration of fever was 7 days. Only in one case blood - culture was reported positive with gram positive cocci. Cerebral toxicity developed in two patients with 22 and 40 years old, and in the latter was irreversible. Six patients died during induction therapy: three of them due to sepsis, one due to intracerebral hemorrhage, one due to ARDS and the last one due to disseminated intravascular coagulation (DIC) (the last two were truly a complication of sepsis). Major additional toxicities are listed in table 2. The overall survival rate from diagnosis was 55.5% (95% CI, 30.8-78.5) at 6 months for the 19 cohort patients and DFS was 50% (95% CI, 26-74). The overall survival rate and DFS for those patients who achieved an initial CR were 85% (95% CI, 51.6-97.9) and 75% (95% CI, 42.8-94.5) at 6 months respectively. Of patients who entered CR, 3 out of 10 patients relapsed at 6 months follow up. Sex was not a risk factor for overall survival (P=0.3) and DFS (P=0.3). Presenting WBC count did not affect death rate (P=0.8). The power of this study was modest (43%).

Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mitus*</th>
<th>Present study</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>94</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>40 years</td>
<td>30 years</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>(7-63)</td>
<td>(20-40)</td>
<td></td>
</tr>
<tr>
<td>Sex M/F</td>
<td>45/64</td>
<td>9/10</td>
<td>0.9</td>
</tr>
<tr>
<td>FAB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1</td>
<td>9</td>
<td>0</td>
<td>0.9</td>
</tr>
<tr>
<td>M2</td>
<td>37</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>M3</td>
<td>15</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>M4</td>
<td>14</td>
<td>7</td>
<td>0.03</td>
</tr>
<tr>
<td>M5</td>
<td>12</td>
<td>5</td>
<td>0.1</td>
</tr>
<tr>
<td>M6</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>M7</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>WBC</td>
<td>7,300</td>
<td>28,910</td>
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</table>

* On admission

Table 2

<table>
<thead>
<tr>
<th>Mitus’ study</th>
<th>Present study</th>
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</thead>
<tbody>
<tr>
<td>Death 7/94 (7%)</td>
<td>Death 6/19</td>
</tr>
<tr>
<td>Bact. Infection</td>
<td>Sepsis 3</td>
</tr>
<tr>
<td>Fungal info</td>
<td>DIC 1</td>
</tr>
<tr>
<td>Intracranial hemorrhage dysfunction</td>
<td>CNS hemorrhage 1</td>
</tr>
<tr>
<td>Cerebral</td>
<td>ARDS 1</td>
</tr>
<tr>
<td>Liver Toxicity</td>
<td>Liver Toxicity 1/19</td>
</tr>
<tr>
<td>(19%)</td>
<td></td>
</tr>
<tr>
<td>Mucositis</td>
<td>Mucositis 2/19</td>
</tr>
<tr>
<td>(39%)</td>
<td></td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>Diarrhea 4/19</td>
</tr>
<tr>
<td>(3%)</td>
<td>Vomiting nausea 2/19</td>
</tr>
</tbody>
</table>

DISCUSSION

The present study was performed with the aims of investigating the toxicity and antineoplastic activity of 3+7+3 regimen in patients with de novo AML. We were faced with 40% failure in standard therapy (14) whilst our time sequential therapy decreased failure rate and achieved an initial CR of more than 80%. Though the final CR was calculated 52.5% for intention to treat analysis, it could not be a disapproval of 3+7+3 protocol. An overview to our data shows that a great number of deaths are due to sepsis during recovery phase of bone marrow (85.7%). On the other hand the overall survival of patients who had achieved a CR and who survived after their marrow recovery was 83.3% at 6 months. In present study just 3 patients relapsed after entering CR, whereas the relapse rate after achieving a CR in patients treated with standard regimen is much higher as reported in literature (14).

The main cause of death in the current study and Mitus trial was infection but by comparison with each other, it is realized that the death rate due to sepsis in the present study is surprisingly greater than that of Mitus. Thus it demands more preventive care and justified.

Of 19 patients enrolled in this cohort study, 7 patients died. Three patients relapsed at 6 months following a CR, 2 patients had refractory AML and just 7 patients really are disease free. One of them received autologous BMT and the additional one is a candidate for it but the optimized donor has not been available as yet.

Bone marrow biopsies on day 17 showed hypoplasia in 87.9% of the patients. Just one patient died before day 17 and three cases did not achieve a CR at that time.
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antibiotic therapy. Of 94 patients in Mitus trial just 7 patients died during induction therapy while this was 6 among 19 patients in the current trial (P=0.001). In both studies, systemic infection was the main cause of death and in all patients fever flared up as a sign of infection.

Of interest, in contrast to prior observations, we could not adequately manage systemic infection despite initial good response. Therefore firstly we should revise the causes of infection in our patients, giving them a good insight about preventive cares including surrounding environment, segregation, oral, skin and anal hygiene. Secondly we have to support our patients to overcome sepsis by using justified antibiotics regarding their clinic and laboratory results, and besides we should recheck the technical aspects of our diagnostic methods. The last one is administering of GCSF just after termination of induction therapy. However a survey to assess the cause of deaths in patients receiving 3+7+3 regimen is necessary, further experience with this regimen will be required to judge its absolute improvement.

REFERENCES


