

Low-dose Cytosine arabinoside; disease free survival and overall survival in the elderly patients with Acute Myeloid Leukemia

Zohreh Sanaat¹, Amin Najafi²

ABSTRACT

Objectives: The median age of the patients with acute myeloid leukemia (AML) is 65 years. Studies have revealed that the prognosis of the elderly patients (over 60 years) is not satisfying. The aim of this study was to evaluate the survival of AML patients being treated with Low-dose Cytosine arabinoside.

Methodology: In this cross-sectional study, 20 AML patients treated with Low-dose Cytosine arabinoside. Disease free survival and overall five-year survival ratios were identified.

Results: In this study there were 11 males (55%) and nine female (45%) with a mean age of 63.3± 18.4 years. The median of disease free survival was 12.4 months and five-year survival was 1.7 years.

Conclusion: Apparently disease-free survival and overall five-year survival in the AML patients being treated with Low-dose Cytosine arabinoside are similar to that of cases being treated with intense chemotherapy regimens.

KEY WORDS: Acute myeloid leukemia; Low-dose Cytosine arabinoside; Disease-free survival; Overall survival; Flowcytometry; Elderly AML.

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INTRODUCTION

Acute myeloid leukemia (AML) is characterized by infiltration of neoplastic cells of hematopoietic apparatus in blood, bone marrow and other tissues. Genetic, radiation and chemical factors and other occupational encounters have been suggested to be influential in AML.^{1,2} One of the factors influencing prognosis is the age of diagnosis which is one of the most important factors in treatment. Old age at diagnosis deteriorates prognosis.³ Almost 60% of

the patients with AML are over 60 at the time being diagnosed. The treatment of the elderly patients is associated with therapeutic difficulties as these people do not respond to conventional regimens and are resistant to treatment.²

On the other hand, co-existing diseases in the elderly reduce their tolerance.^{2,3} It has previously proved that low doses of Cytosine arabinoside with the same efficacy of the more invasive treatments can be administered in AML patients, especially in the elderly.⁴ Evaluation of disease-free survival and overall survival in patients with AML is of great importance. The objective of this study was to evaluate disease-free survival and overall survival ratios in AML patients being treated with Low-dose Cytosine arabinoside.

METHODOLOGY

In a cross-sectional and descriptive analytic study, from March 1995 through February 2005, 20 untreated AML patients older than 60 were selected

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who were diagnosed in Shahid Ghazi Tabatabaei Hematology and Oncology ward of Tabriz University of medical sciences -Iran .We recovered our data from medical records. None of the patients had a history of prior therapies with antineoplastic drugs or a diagnosis of myelodysplastic syndrome. All patients of this study received a unique medical treatment which was low-dose Cytosine arabinoside 20 mg twice a day for 15 days. Those patients who achieved complete remission (CR).

Complete remission is defined by; absolute neutrophil count of 1500 per millimeters square or more Platelet count of 100000 per millimeters square or more, no blast in circulation. Hematopoietic cell population of bone marrow more than 20% with major three lineage proliferation, blasts of bone marrow less than 5% without Auer rod, no extramedullary leukemic foci. The immunophenotype was performed by multiparameter flowcytometry (FACSCalibur flow cytometer, Becton Dickinson, California, US). Flowcytometry was performed on blast cells of bone marrow gated on their abnormal light scatter characteristics using mAbs for the following 16 antigens: CD13, CD14, CD15, CD33, CD11b, CD19, CD20, CD2, CD3, CD7, CD10, CD34, CD45, HLA-DR and Glycophorin-A. A membrane marker was considered positive when more than 15% of the blast cells expressed it.

Disease free and overall five-year survival were determined in these patients. SPSS-13 statistical software was used. To compare quantitative data Kruskal-Wallis test and to determine Post Hoc, Mann-Whitney test were used. Survival ratio was calculated using Kaplan-Meier curves. Except for interpretation of the results obtained from Post hoc, $p \leq 0.05$ was considered significant.

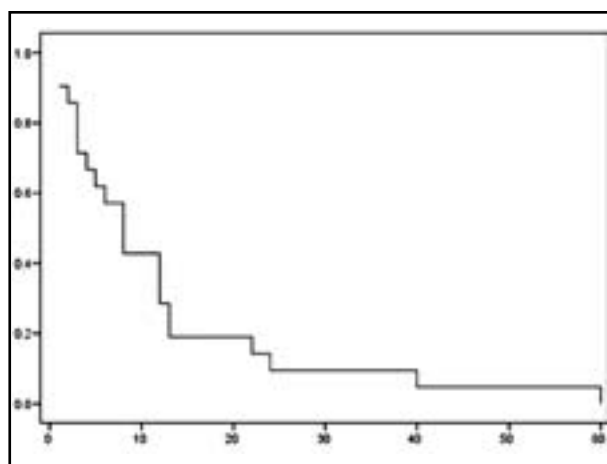


Fig-1: Kaplan-Meier product-limit estimate of disease free survival (days)

RESULTS

In this study there were 11 males (55%) and nine females (45%) with a mean age of 63.3 ± 18.4 years. Among different markers, the most positive markers were the following: the myeloid lineage antigens CD13 (38%), CD33 (38.1%), and the hematopoietic progenitor cell markers HLA-DR (46.1%), and CD34 (28.6%). CD7 was positive in 14.3% of the patients.

Disease-free survival according to the gender of the patients: there was no statistically significant difference in gender groups regarding disease-free survival ($p = 0.336$). Disease -free survival according to the age of the patients: there was no statistically significant difference in age groups regarding disease-free survival ($p = 0.126$). Kaplan - Meier curve for disease-free survival and overall survival are demonstrated in Figure-1 and 2.

DISCUSSION

We evaluated disease-free and overall survival ratios in AML patients being treated with Low-dose Cytosine arabinoside. The mean disease-free survival was 12.4 months and overall five-year survival was 9.5% with a mean of 1.7 years. Administering low-dose Cytosine arabinoside has been previously proved to have considerable effects on acute leukemia treatments in different studies.⁵⁻¹² Fridrik et al in a study carried out on 6 AML patients being treated with low-dose Cytosine arabinoside reported a variable overall survival ratio of 16 to 55 months.¹³

Powell et al carried out a study on 38 AML patients being treated with Low-dose Cytosine arabinoside. The disease-free survival median was reported 9.8 (with a range of 2.4-17.9) months and overall

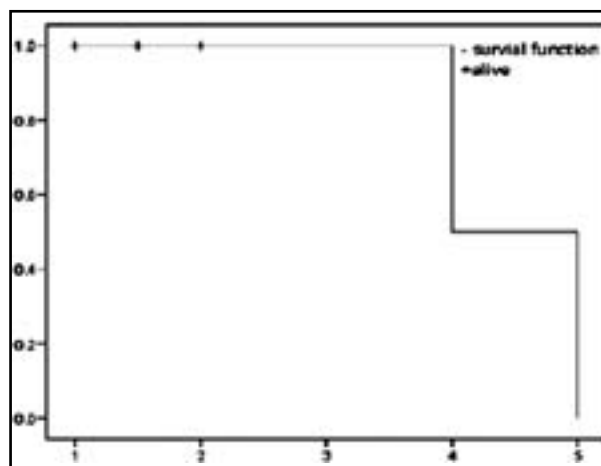


Fig-2: Kaplan-Meier product-limit estimate of overall survival (years)

survival median was 15.7 (with a range of 6-22.7) months.¹⁴ In a study carried out by Nair et al on 28 patients with acute myelodysplastic syndrome all patients were treated with low-dose Cytosine arabinoside. Only did two patients (7.1%) survived for more than two years.¹⁵ In the study of Robles et al which was carried out on 41 AML patients being treated with low-dose Cytosine arabinoside, the mean disease-free and overall survival ratios were reported to be 7.4 and 10.9 months respectively.¹⁶

Burnett et al in their study carried out on 217 AML patients being treated with low-dose Cytosine arabinoside 28 mg twice a day for 18 days, overall survival ratio in eight weeks, one year, two years and three years were reported to be 61%, 13%, 4% and less than 1% respectively.¹⁷ Qian et al conducted a study to evaluate the effect and toxicity of the low-dose Cytarabine and Aclarobisin in combination with G-CSF (CAG regimen) in elderly AML patients. Fifty patients were included in the study with an overall response ratio of 72%. 29 patients experienced complete remission. The mean survival ratio was 14 months in this study.⁴

As it can be observed, the mean disease-free survival and overall survival obtained from our study are also in the above-mentioned limits. Five-year survival of the patients in the present study have, however been reported to be higher compared to other studies. Varied reasons may have affected disease-free and overall survival in this group of the patients which can explain the different ranges reported in our study. As it can be seen most of the mentioned studies in this field are not recent and novel achievements may play a role in increasing survival of these patients.

Burnett et al however have emphasized on the non-significant changes in the survival of these patients within recent decades.¹⁷ Differences in the demographic specifications of patients including age and gender may also be influential. In this study we evaluated the effect of each two factors separately on disease-free and overall survival. No statistically significant difference was observed between male and female patients in this regard. According to our investigations no similar study has been carried out in this regard so far. On the other hand Satou et al in their study, showed that low-dose Cytosine arabinoside is appropriate in elderly AML patients resistant to treatment.¹⁸ Tilly et al achieved similar results in this regard. In this study, 41 AML patients older than 65 years old were studied and finally it was concluded that final results obtained from this therapy are similar to invasive therapies.¹⁹

It should be mentioned that the indication for being treated by low-dose Cytosine arabinoside in the present study is the age over 60. Low sample volume is one of the major limitations of the present study. Overall the present study can be considered a unique study regarding evaluating the effect of low-dose Cytosine arabinoside on AML patients older than 60 years old and their overall five-year survival.

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