Open Access Original

Journal of Renal Endocrinology

J Ren Endocrinol 2024;10:e25134.
https://www.jrenendo.com
doi: 10.34172/jre.2024.25134

Nickan Research Institute

Factors affecting the survival of patients with refractory and relapsed acute myeloid leukemia

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Abstract

Introduction: Acute myeloid leukemia (AML) is one of the poor prognostic diseases. It relapses in more than half of young and 85% of old patients. AML patients with good prognosis are candidates for transplantation in the second remission and patients with poor or intermediate prognosis are candidates in the first remission.

Objectives: In this study, the survival of patients with AML, and the effect of bone marrow transplantation (BMT) were evaluated.

Patients and Methods: This retrospective study was carried out on 30 patients with relapsed and refractory AML who were admitted to Taleghani Hospital. The overall survival (OS) rate and effective factors (WBC count, platelet count, cytogenesis) were determined. Collected data were analyzed by using version 24 of SPSS and via appropriate statistical tests. $P<0.05$ was considered statistically significant.

Results: Thirty patients—56% with refractory AML and 43% with relapsed AML—were enrolled in the study. Complete remission was achieved in 23% of patients, the others did not achieve remission despite salvage chemotherapy. Relapse-free survival (RFS) in these patients was 12±1weeks. Only 3% of patients received BMT. There was a statistically significant association between WBC count, platelet count, cytogenesis study, and OS.

Conclusion: Relapsed or refractory AML is a disease with a very poor prognosis, despite salvage therapy. So, we recommend that all patients with AML should receive BMT in their first remission.

Keywords: Acute myeloid leukemia, Disease-free survival, Survival rate, Platelet count, White blood cell count

Citation: Ghazizadeh M, Ghazizadeh M. Factors affecting the survival of patients with refractory and relapsed acute myeloid leukemia. J Ren Endocrinol. 2024;10:e25134. doi: 10.34172/jre.2024.25134.

Introduction

Acute myeloid leukemia (AML) is one of the poorest prognostic diseases worldwide (1). More than half of young patients and 85% of old patients do not achieve remission or relapse (2). In general, AML patients with good prognoses are candidates for transplantation in second remission, and patients with poor and intermediate prognoses are candidates for transplantation in first remission (3,4). The outcome of bone marrow transplantation (BMT) is related to several factors, such as blast counts, platelet counts, and white blood cell (WBC) counts at the time of diagnosis; cytogenesis; response to induction chemotherapy; and the number of CD34-positive cells at the time of diagnosis (5). In one study performed by Damiani and colleagues, 72 patients with relapsed and refractory AML who received BMT were followed for 5 years. Sixteen percent of patients were alive, 74% died because of post-transplantation infections, and 9% died because of graft-versus-host-disease (6). A good performance status and a full match donor result in improved overall survival (OS) (7). In another study performed by Weltermann and colleagues, 255 patients with relapsed and refractory AML who received BMT were enrolled (8). After 5 years of follow-up, 80% of the patients in the low-risk subgroup and 52% of the patients in the high-risk subgroup were alive. Complete remission after induction chemotherapy was the most important prognostic factor after BMT. Patients who received BMT with minimal residual disease had poor prognosis after BMT (9). In another study performed by Kern and colleagues, the authors concluded that patients whose relapse occurred more than one year after complete remission had a better prognosis after salvage chemotherapy and BMT (10). They also concluded that patients with good cytogenesis had better outcomes after BMT than patients with poor or intermediate cytogenesis.

Objectives

This study was designed to evaluate the OS of patients with relapsed and refractory AML and the possible prognostic factors.

Patients and Methods

Study design

This retrospective study including 30 patients with

Received: 15 September 2023, Accepted: 16 February 2024, ePublished: 9 March 2024

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Implication for health policy/practice/research/ medical education

Acute myeloid leukemia (AML) is one of the poorest prognostic diseases in the world. The white blood cell (WBC) count, platelet count, and hemoglobulin concentration are prognostic factors that can affect a patient's overall survival (OS).

relapsed and refractory AML treated at Taleghani hospital for a three-year period. Patients who were more than 60 years old, had acute promyelocytic leukemia, or had Karnofsky scores less than 70 were excluded. The diagnosis of AML was based on more than 20% blasts according to the bone marrow blast count (according to the WHO index). Information on patients with refractory AML and relapsed AML was collected from their files. The included variables were hemoglobin (Hb), WBC and platelet count at diagnosis and the kind of salvage therapy that was prescribed during the relapse phase or between the distance of disease relapse and BMT or death.

Statistical analysis

Patient information was analyzed by using the t test and chi-square test in version 24 of SPSS via appropriate statistical tests. A P value < 0.05 was considered to indicate statistical significance.

Results

Thirty patients with refractory and recurrent AML were evaluated (Table 1). The average age of these patients was 34 ± 9 years. Seventy-six percent of these patients were men, and 34% were women. Twenty-two patients were less than 40 years old. The OS was 10 ± 11 weeks in patients younger than 40 years and 6 ± 7 weeks in patients older than 40 years. Moreover, there was no significant difference in OS between these two groups (P = 0.3). The minimum number of WBCs in these patients was 3000/μL, and the maximum number was 154 000/μL. The mean WBC was 50 000/μL ± 40 000/μL. The OS in patients with WBC<30 000/μL was 12±14 weeks and in patients with WBC >30 000/μL was 6±5 weeks, so there was a significant difference in the OS between WBC<30 000/μL and WBC >3000/μL (P = 0.01). The patient's Hb concentration was less than 8 g/dL in the minimum state and 11 g/dL in the maximum state. The OS was 11±3 weeks in patients with Hb>8 g/dL and 5±6 weeks in patients with Hb<8 g/dL. There was a significant difference in OS according to Hb level (P = 0.03). The platelet count was between 13 000/μL and 188 000/μL, with an average of 51 000±39 000/μL. Eighty percent of patients had platelet counts less than 80 000/μL. There was a significant difference in OS between patients with platelet counts less than or greater than 80 000/μL (P = 0.03).

Out of 30 patients enrolled in the study, 8 patients (27%) had primary refractory AML. These patients did not achieve remission with any kind of chemotherapy. Nine patients (30%) had relapsed less than 6 months after chemotherapy (early relapse), and 13 patients (43%) had relapsed more than 6 months after chemotherapy (late relapse). The minimum relapse-free survival (RFS) in these patients was one week, and the maximum RFS was 48 weeks. The average RFS was 12±11 weeks. The median OS in patients with relapsed and refractory AML was 9±10 weeks. All of the relapsed and refractory AML patients in our study received salvage chemotherapy (Table 2). Finally, 23% of patients achieved remission with salvage chemotherapy, and 77% of patients did not achieve remission with any type of salvage chemotherapy. There was no significant difference in the point of remission between the kinds of salvage chemotherapy (P = 0.5). Only one patient received BMT. The reason was the lack of a matching donor and the complications of salvage therapy, especially sepsis, which led to death before transplantation. Additionally, 83% of patients died.

Discussion

According to the current study, OS was decreased in patients with a WBC >30 000/μL. Therefore, there was a significant difference in the OS rate according to the WBC count. This finding was compatible with the findings of previous studies (4). In our study, we found a direct correlation between Hb concentration and OS, however this correlation was not confirmed by any of the other studies. Additionally, we found a correlation between the platelet count and OS. OS decreased in patients with platelet counts less than 80 000/μL. Zhang et al reported that patients with a PLT between 50 000/μL and 120 000/μL had better overall and disease-free survival (11). The pretreatment platelet count is an important prognostic

Table 1. Statistical descriptions of the studied variables among 30 AML patients

Variables	Minimum	Maximum	Mean	SD
Age (y)	17	51	34.3	9.5
WBC (/μL)	3000	145 000	50.0	41.3
Hb (g/dL)	5	11	8.1	1.2
PLT (/μL)	13 000	188 000	15.1	39.8
Overall survival (wk)	1	48	9.2	10.6

WBC, White blood cell; Hb, Hemoglobin; PLT, Platelet count; SD, standard deviation.

Table 2. Chemotherapy regimens used in salvage therapy

Chemotherapy regimens	Number	Valid Percent
7+3	9	30
EMA	14	46.7
FLAG	4	3.13
Others	3	10
Total	30	100

EMA: Etoposide, Mitoxantrone, Cytarabine; FLAG: Fludarabine, Cytarabine, Filgrastim.

factor for OS, and early recovery of the platelet count after induction chemotherapy has been associated with longer OS (12). We divided the patients into three groups: primary refractory, early relapsed (relapse in less than 6 months) and late relapsed (relapse in more than 6 months). The highest mortality rate was observed in refractory patients (88%). This part of the study was compatible with Weltermann and colleagues (8). In this study, the achievement of complete remission after induction chemotherapy was the most important prognostic factor in recurrent AML patients. In our study, the prognosis of patients who experienced late relapse was better than that of patients with primary refractory disease. The complete remission rates after salvage chemotherapy in the late relapse group and the primary refractory group were 30% and 17%, respectively. This finding was similar to that of Kern and colleagues' study (10). According to Martin's study, complete remission was 55-60% in patients with late relapsed AML and 33-46% in patients with early relapsed AML. These results were better than those of the present study. In our study, 17% of patients in the late relapse group received BMT, but among the refractory AML patients, only one patient received BMT. In the study performed by Fong and colleagues, 38% of patients with relapsed AML received BMT after salvage chemotherapy (2). This was because of the lack of matched donors in our study and the presence of complications associated with salvage chemotherapy, such as sepsis. In addition, these patients are more susceptible to lethal infections due to immunosuppression (1). Therefore, most of the patients died before receiving transplantation.

We found that despite salvage chemotherapy in patients with relapsed and refractory AML, the prognosis was poor. Similarly, the frequency of performing BMT was lower in these patients than in those in similar studies. Accordingly, our recommendations for improving patient survival include the following entities:

- All of the AML patients received BMT in remission.
- BMT centers should be expanded so that more patients can undergo BMT.
- Since 50% of patients did not receive BMT due to a lack of suitable donors, we should expand the bank of stem cells.

Conclusion

The mortality rates of patients with late relapse and primary refractory AML were high in the present study. Possible prognostic factors are the WBC count, platelet count, and hemoglobulin level, which can affect OS. These factors should be considered when choosing the appropriate treatment options, especially in patients receiving BMT.

Limitations of the study

The study's retrospective design served as its primary limitation. To ensure more reliable results, a prospective case-control study should be considered for future research.

Authors' contributions

Conceptualization: Maryam Ghazizadeh, Matin Ghazizadeh.
Data curation: Maryam Ghazizadeh.
Formal analysis: Maryam Ghazizadeh.
Funding acquisition: Maryam Ghazizadeh, Matin Ghazizadeh.
Investigation: Maryam Ghazizadeh.
Methodology: Maryam Ghazizadeh.
Project administration: Maryam Ghazizadeh, Matin Ghazizadeh.
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Supervision: Matin Ghazizadeh.
Validation: Maryam Ghazizadeh.
Visualization: Matin Ghazizadeh.
Writing–original draft: Matin Ghazizadeh.
Writing–review and editing: Matin Ghazizadeh.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The study adhered to the principles of the Declaration of Helsinki. Approval for this research was granted by the Ethics Committee of Shahid Beheshti University of Medical Sciences under ethical code #IR.SBMU.MSP.REC.1401.492. Subsequently, written informed consent was acquired from all participants prior to any interventions. All the ethical issues (including plagiarism, data fabrication, and double publication) have been completely observed by the authors.

Funding/Support

The authors declare that they have no funding support.

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