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Prognostic Evaluation in Patients with Acute Myeloid Leukemia, From Diagnosis to Treatment: A Single-Center Experience

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ABSTRACT

A total of 124 patients followed-up with the diagnosis of AML with known clinical, laboratory, and flow cytometry results in 2016-2019 were retrospectively examined. Sixty nine of the cases (55.6%) were male and 55 (44.3%) were female. The average age at the time of diagnosis was 53.44±30.3 years old. The median follow-up time was 856 (143-1276) days. It was found that presences of >60 age, male gender, non-APL AML, bcr-abl positivity, recurrence, and requirement of re-induction were related to lower survival. The time between diagnosis and therapy was longer at the patient group unresponsive to therapy. The median follow-up duration was 856 (143-1276) days and 74 of our patients (59.6%) are alive. We detected in our study that the flow cytometry results and the short time to initiation of therapy possibly affect the response to therapy. The immunophenotype and genetic results may be combined to have an idea of prognosis and may affect therapy regimen preference.

Keywords: Acute Myeloid Leukemia; Factors Affecting Survival; Genetic Risk; Prognosis

Introduction

AML is a heterogeneous, hematologic malignancy that is characterized byclonal expansion of early myeloid progenitor cells on peripheral blood, bone marrow, and/or other tissues (such as sarcoma) and that may cause a short survival for reasons like infection, bleeding, leukocytosis if untreated [1,2]. World Health Organization has updated the AML classification to include morphology, immunophenotyping, cytogenetics, and molecular characteristics, and their reasons in 2016 [3]. Many factors related to the patient and the tumor such as >60 age, poor prognosis, presences of Philadelphia chromosome, dysplasia and extramedullary disease, monosomy in 5th and 7th chromosomes, complex karyotype, FMS-like tyrosine kinase 3 (FLT3) mutation, MLL partial tandem duplication, secondary AML, slow response to cytoreduction, and over1 chemotherapy sessions to have a complete response were associated with poor prognosis [4-8]. Also,

the time between diagnosis and therapy was found to be important in response to therapy and survival [9] while it was found as irrelevant in some studies [10]. Our study aims to determine the effects of flow cytometry and genetic results of our patients with AML, to evaluate the factors that affect therapy regimen and the response to therapy, to present advice on regimen preference, and to contribute to the literature.

Methods

Compliance with Ethical Standards

The ethical approval for the study was obtained from the ethics committee of NEU Meram Medical Faculty (decision date: 05.02.2021 and no. 2021/3060).

Study Design

A total of 124 patients, whose clinical, laboratory, genetic, and flow cytometry results were known at the time of diagnosis and who were followed-up with the diagnosis of AML in the adult hematology clinic of NEU Meram Faculty of Medicine between 2016 and 2019, were included in our study. The effects of demographic, clinical, cytogenetic, and molecular characteristics in patients with the diagnosis of AML and therapies of AML induction and consolidation on overall survival (OS) and progression-free survival (PFS) were retrospectively examined.

Statistical Analysis

The descriptive statistics related to numerical variables were presented as mean standard deviation or median (q1-q3). Nominal variables were presented as frequency (percentage). T-test or ANOVA was used to compare the numerical variables. A Chi-square test was applied for the categorical variable. The Cox regression method was used to find the variables related to OS and PFS. Kaplan Meier method was used to draw survival curves. Analyses were made with SAS University Edition 9.4 program. $P<0.05$ was accepted as significant.

Results

Sixty-nine of the cases (55.6%) were male and 55 (44.3%) were female. Twenty one of 124 cases (16.9%) had acute promyelocytic leukemia (APL) and 1 had biphenotypic leukemia. Seven (5.6%) had a history of myelodysplastic syndrome, 1 had essential thrombocytosis, 1 had chronic myeloid leukemia, 1 had sarcoma, 2 had breast cancer, 1 had prostate cancer and 1 had a colon cancer history. One of our patients was at the 18th week of pregnancy at the time of diagnosis. Three patients had lymph nodes,1 had gingival, and 1 had colon involvements. The average age at the time of diagnosis was 53.44±30.3 years old. The average age in APL was 40.9±14.7 and it was 55.8±31.9 in non-APL AML. FISH (Fluorescent In Situ Hybridization) analysis at diagnosis revealed abnormalities in 62 patients (50.8%). Karyotype analysis revealed normal karyotype at 72 patients (60%), any type of abnormality in 32 patients (26.6%) but it was insufficient in 16 of the cases (33%). Molecular test results showed BCR-ABL positivity in 4 patients (3.7%) and PLM-RARA positivity in 14 patients (13%). We were able to check FTL3 in 18 patients and CCAAT/enhancer-binding protein alpha (CEBPA) in 5 patients. They were positive in 1 patient each (5.5% and 20%, respectively) while nucleophosmin-1 (NPM1) that we were able to check-in 11 patients were negative in all. 34 (27.4%) were at the good, 61 (49.2%) were at moderate, and 29 (23.4%) were at poor-risk groups according to the 2017 European Leukemia Net genetic risk analysis recommendations. 49.1% of patients (n:59) had CD34, 96.7% (n:118) had CD45, 74.1% (n:89) had HLA-DR and 67.3% (n:66) had CD117 leukemia. Of the patients, 31.6% (n:38) had CD7, 57.8% (n:37) had CD11c, 73.5% (n:86) had CD13, 17.5% (n:21) had CD14, 39.1% (n:47) had CD15, 85.8% (n:103) had CD33, 30.2% (n:23) had CD68, 8.1% (n:8) had glycophorin a, and 57.5% (n:69) had MPO leukemia. The time before the initiation of therapy was a median of 4 (2-7) days. The reasons for the delay in therapy were the rejection of treatment, infectious causes like pneumonia, herpes, salmonella, or tuberculosis, and the presence of conditions requiring surgery like urinary stones and rectal abscess.

The median follow-up time was 856 (143-1276) days. The median follow-up duration was 1304 (574-1906) days for the (n:34), 464 (156-1062) days for the moderate risk group (n:61), and 344 (103-734) days for the poor-risk group (n:29). Idarubicin-low dose cytarabine regimen was administered to 81 patients (65.3%), high dose cytarabine (HIDAC) to 2 patients (1.6%), hypomethylating agent to 19 patients (16%), ATRA-idarubicin to 21 patients (16.9%), and GRAALL-2003 regimen was administered to 1 patient (0.8%). Seventy-three patients were responsive to the induction regimen (61.3%) while 46 were unresponsive (38.6%). Five patients died before completing the regimen. The response rates to induction regimen were found as follows: 56.7% for idarubicin-low dose cytarabine regimen receivers, presence of response in 2 patients receiving HIDAC. The response rate to hypomethylating agents was 22.2% (Table 1). Thirteen patients who were administered a hypomethylating agent and 4 patients who were administered intensive induction therapy died before we could evaluate a response to the reinduction therapy. 2 patients rejected the therapy. Twenty-seven patients who were administered a reinduction regimen were evaluated and 17 patients (62.9%) had remission. Seven patients received idarubicin-cytarabine (25.9%), 16 had HIDAC (59.2%),3 had fludarabine, cytarabine, and G-CSF (FLAG) as reinduction regimens; 3 patients had more than one regimen and differently, 4 had cladribine, mitoxantrone, etoposide, hypomethylating agent. The response rate was 14.2% in the group

who received idarubicin-cytarabine as the reinductionregimen, 81.2% in the HIDAC-receiving group, and 33% in the FLAG-receiving group (Table 2). Recurrences were detected in 23 patients (24.4%) and the median time to the recurrence was 933 (270-1285) days. Recurrences were observed as 21.4% in the ones receiving idarubicin-low dose cytarabine regimen; 27.2% in hypomethylating agent-receiving ones, 1 of 2 patients in HIDAC-receiving patients, and in 2of ATRA-idarubicin receiving ones. It was seen that 40.3% were dead after examining the analysis of the final condition via an induction regimen. The examination according to the regimens revealed 40.5% deaths in patients receiving idarubicin-low dose cytarabine, 1 death in HIDAC receivers, and 73.6% deaths in hypomethylating agent receivers. It was seen that 59.2% were dead after examining the analysis of the final condition via a reinduction regimen. The examination according to the regimens revealed 60% deaths in patients receiving idarubicin-low dose cytarabine, 42.8% death in HIDAC receivers. 3 patients receiving FLAG died.

Allogenic bone marrow transplantation was performed on 31 patients (25.4%). The survival was higher in the ones who underwent allogeneic bone marrow transplantation ((p:0.02) (HR: 0.43 (0.19-0.85)). Expressions of CD7, CD11c, CD117, glycophorin-a, CD13, CD14, CD15, CD33, CD45, CD68, HLA-DR, and MPO were found to be unrelated to the response to therapy. CD34 expression was median 33 (6-61) in the unresponsive group and 11 (1-54) in the responsive group and it was statistically significant (p:0.04). Any relationship between myeloid marker positivity, HLA-DR, and CD34 positivity was not found. The time between diagnosis and therapy was median 6 (2-9) in the unresponsive group and 4 (1-6.5) in the responsive group and it was statistically significant (p:0.02). If this time was <3 days, OS was 766 days (152-1464), the median was 792 days (431-1301) for3-5 days, and 356 (122-973) for >5 days. For <60 years of age, if it was <3 days, OS was 1035 days (488-1948),808 days (533-1199) for 3-5 days, 545 days (166-1177) for >5 days. For ≥60 years of age, if it was <3 days, OS was 225 days (64-728), 615 days (330-1535) for 3-5 days, and 132 days (91-642) for >5days. CD68 expression at diagnosis was median 0.5 (0-3) in the group with recurrence and 8 (1-60) in the group with no recurrence and it was statistically significant (p:0.02). Recurrence in the group with CD68 negativity was higher even though no statistical significance was found (HR: 3.3 (0.84-30.9)). Recurrence was lower in the group with the copositive HLA-DR and CD34 and with the copositive myeloid marker (72.4% - 27.6%; 78.57% - 21.43%, respectively). No risk group was determined related to CD7, CD117, glycophorin-a, and CD34 leukemia. >60 years of age at diagnosis (p<.0001, HR: 3.31 (0.18-0.56)), male gender (p:0.01 HR 2.1 (1.2-3.97)), detection of non-APL AML (p:0.007 HR 9.3 (2.52-82.8), long duration between diagnosis and therapy (p:0.03 HR:1.046 (0.999-1.086)), requirement of reinduction (p:0.03) and presence of recurrence (p:0.0099 HR:2.158 (1.188-3.812)) were found to be related to lower survival. It was determined that presences of PML-RARA (p:0.03) and response to induction therapy (p:0,0001 HR:0,15(0,078-0,283)) and reinduction regimens (p: 0,0075 HR:0,242 (0,084-0,656)) were associated with higher survival (Table2). No relationship between myeloid marker copositivity, HLA-DR and CD34 copositivity, and survival was detected. It was found that survival was associated with the genetic risk group (p<.0001) (Figure 2). The final condition analysis reveals that 74 patients (%59.6) are alive (Figure 3).

Discussion

Most of the AML cases are observed at >60 years of age [11-13] and more frequently in men. 13-14 Thirty- five% of our patients were >60 years old and the disease was more frequent in men. Survival in the male gender and at an older age was observed at a lower rate by the literature. The survival rate >60 years old was 43% while the survival rate was 59.6% (Figure1). Multi parameter flow cytometry is used in the diagnosis of acute leukemia [11,15,16]. Myeloid and lymphoid markers are used for diagnosis and also, CD45, CD34, or CD117 are used to determine the blast ratio [17]. The coexistence of CD34 and HLA-DR is an individual predictor marker about the failure of remission [18]. Several studies associated CD7, CD19, CD11b, CD13, CD14, CD33, CD34, CD56, and TdT with poor results. Legrand et al. detected higher rates of remission and survival in the presence of the pan-myeloid marker in their study [19]; however, Üsküdar Teke et al. did not reveal this relationship in their study [20]. The recurrence rate was lower in myeloid marker and HLA-CD34 copositive patients despite the statistically in significant relationship even though no relationship was determined between the cell surface markers and survival in our study. We determined that response to therapy was associated with a lower CD34 expression and higher CD68 negativity was associated with recurrence. François et al. showed that the percentage of CD34 (+) CD38 (low / -) CD123 (+) leukemia cells and the response to therapy and survival significantly correlated in one of their studies [21]. This conclusion conforms to our conclusion. We did not find any data reviewing the recurrence risk with CD68 in the literature. 27.4% of the patients were at a good, 49.2% were at moderate, and 23.4% were at poor-risk groups according to the 2017 European Leukemia Net genetic risk analysis recommendations. Pastore et al. detected more relapse and lower OS in the poor genetic risk group in one of their studies [22]. We determined in our study OS as 85% in the good-risk group, 52% in the moderate-risk group, and 44% in the poor-risk group (Figure 2). We did not find an association in our study even though some surface markers and genetic risk groups are associated [23]. The time before the initiation of therapy was a median of 4 (2-7) days in our study.

Lower response to therapy was found with a longer time before the initiation of therapy and no relationship with the overall survival was found in an ECOG study conducted with AML patients older than 55 years old [24]. In another study, no relationship was found between OS and remission rates in patients older than 60 years old while in younger patients, lower remission and survival rates were determined with the time as 5 days or shorter [9]. Röllig et al. found that this duration was not related to OS in their study [10]. We determined lower responses to therapy and shorter OS with a long time between diagnosis and therapy. AML therapy includes induction and post-remission therapies. The induction therapy aims to have complete remission preferably without a measurable residual disease. The complete response to the anthracycline-based regimen is 80% in the patients at good risk group and 50-60% in moderate-risk group patients in the literature [25]. The complete remission rate in the poor-risk group is only about 40% and the median overall survival is between the range of 12-18 months [26]. We had a response to the induction regimen of 61.3% in our study in accordance with the literature. The response rates based on regimen were found as follows: 65.3% for idarubicin-low dose cytarabine regimen receivers, presence of response in 2 patients receiving HIDAC. The response rate to hypomethylating agents was 22.2%. The number of patients who were administered HIDAC was low. Our study supports the use of idarubicin-low dose cytarabine which has been used for more than 50 years. There is no common idea on the optimal regimen for relapsed/refractory patients. The same regimen maybe administered to the patients who have been in remission for more than 1 year after the idarubicin-cytarabine regimen and about 50% of response can be achieved [27,28]. HIDAC maybe effective in 35% to 40% of idarubicin-cytarabine-resistant patients [29]. The complete response rate in primary refractory/relapsed AML patients is 45-55% for FLAG regimen [30,31]. We used mainly idarubicin- cytarabine (25.9%) and HIDAC (59.2%) administration in our study. The response rate was 14.2% in the group who received idarubicin-cytarabine as the reinduction regimen, 81.2% in the HIDAC-receiving group, and 33% in the FLAG-receiving group. The high response rate received by the HIDAC regimen was remarkable in our study.

Study Limitations

Although our total number of patients is sufficient, the limitation of our study is that it is a single center and retrospective. We think that if the number of patients receiving a reinduction regimen is increased, it will make a significant contribution to the literature on the regimen.

Conclusion

We think that patient's condition should be stabilized, and treatment should be initiated immediately while tests of prognostic value are applied in the therapy plan of AML. Besides, HIDAC may be selected as the main induction/reinduction regimen especially in cases where anthracycline cannot be selected due to the detected relative high response rate when we used it as the reinduction regimen even if the number of patients given HIDAC is insufficient.

Ethics

Ethics Committee Approval

All the ethical considerations were strictly followed in accordance with the 1964 Declaration of Helsinki. As standard care/action of the hospitals of the Meram Medical School, it has been recognized from the patient records that all the studied patients had given informed consent at the time of hospitalization and before the administration of chemotherapy and other relevant diagnostic/ therapeutic standards of care. The ethical approval for the study was obtained from the ethics committee of NEU Meram Medical Faculty (decision date: 05.02.2021 and no. 2021/3060).

Informed Consent

Retrospective study.

Authorship Contributions

Surgical and Medical Practices: S.Y., Ö.Y.; Concept: S.Y, Ö.Ç., M.S.Y., A.Z.; Design: S.Y, Ö.Ç., M.S.İ.; Data Collection or Processing: S.Y.; Analysis or Interpretation: M.S.İ., S.Y.; Literature Search: S.Y., Ö.Ç.; Writing: S.Y., Ö.Ç.

Conflict of Interest

No conflict of interest was declared by the authors.

Financial Disclosure

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Conflict of Interest

We certify that we have taken all necessary permissions from our institution and/or department for conducting and publishing the present work. There is no ethical problem or conflict of interest. We declare that this manuscript represents valid work and that neither this manuscript nor one with substantially similar content under the present authorship has been published or is being considered for publication elsewhere and the authorship of this article will not be contested by anyone whose names are not listed here, and that the order of authorship as placed in the manuscript is final and accepted by the co-authors.

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