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Acute Myeloid Leukemia; Experience at a Resource Limited Health Care Facility of Pakistan

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Abstract

Objective: To determine the demographics and clinical outcomes of remission induction in Acute Myeloid Leukemia in settings with limited resources.

Methodology: A retrospective study was conducted at the Department of Medical Oncology, Pakistan Institute of Medical Sciences (PIMS), Islamabad, from January 2005 to April 2022. A total of 334 patients with AML were reviewed for age, gender, address, HBV/HCV status, peripheral film, bone marrow biopsy, flow cytometry, gene markers, cytogenetics, treatment, and outcome. Data was analyzed using SPSS version 25.

Results: AML was predominant in adults with a median age of 30, with 193 (57.8%) in the age group of 19-40 years, followed by 67 (20.1%) in the age group of 12-18 years, 58 (17.4%) in the age group of 41-60 years, and 16 (4.8%) in elderly patients above 60 years of age. Males were affected more compared to females, accounting for 191 (57.2%) vs. 143 (42.8%). Patients from Punjab accounted for 150 (44.7%) of all cases, followed by AJK 75 (22.5%) and KPK 68 (20.4%). Among all 334 patients, 32 (9.6%) had white blood cells above 100,000, and 252 (75.4%) had more than 20% blasts in peripheral film. Out of 334 patients, 260 (77.8%) were diagnosed with AML, 72 (21.6%) with APML, and 2 (0.6%) with MPD transformed to AML. All patients received remission induction chemotherapy, and 93 patients died during induction, resulting in a treatment-related mortality (TRM) of 27.3%.

Conclusion: Acute myeloid leukemia in the Pakistani population is seen in a relatively younger age group with male predominance, and overall induction-related mortality is high in our setup.

Key Words: Acute Myeloid Leukemia, Acute Promyelocytic Leukemia, Induction-related mortality.

Introduction

Acute myeloid leukemia (AML) is the most common acute leukemia in adults but still it accounts for just 1% of adult cancer deaths in United States.[1] The worldwide median age at the time of diagnosis is 65 years.[1] Acute myeloid leukemia (AML) has an incidence which increases with age[2], historically high mortality rates[3], and poor prognosis.[4]

AML is diagnosed on bone marrow aspiration and biopsy showing at least 20% blasts in the bone marrow or peripheral blood. Exceptions that are considered diagnostic of AML without percentage of bone marrow blast include leukemias with certain specific genetic abnormalities, myeloid sarcoma and central nervous system involvement with myeloblasts.[5] Flow cytometry immunophenotyping is used to identify cell membrane antigens.[6] Cytogenetic and molecular genetic findings are the major independent prognostic markers in AML to determine chemotherapy response and outcome.[7]

Several clinical findings help to predict the achievement of complete remission and subsequent disease free survival. Young age[8], good performance status[8] and dysplasia on bone marrow[9] are considered favorable factors.

Acute myeloid leukemia is categorized in favorable, unfavorable, and intermediate risk groups on the basis of molecular and cytogenetic findings. The best treatment for the intermediate risk group is uncertain, favourable risk patients are treated with standard chemotherapy, while patients in unfavourable risk category should undergo allogenic stem cell transplant after remission induction.[2] The 7+3 regimen in AML treatment remained the backbone of standard therapy for close to five

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decades.[10]

Acute pro myelocytic leukemia accounts for 5-10% of AML, it has a distinct clinical presentation associated with disseminated intravascular coagulation and must be diagnosed promptly, and needs immediate treatment that differs from other categories of AML. The administration of all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) modifies APML from being highly fatal to highly curable.[11] The APL0406 study showed that the advantages of ATRA-ATO over ATRA chemotherapy increase over time and that there is significantly greater efficacy in non-high-risk APL patients.[12] For high-risk patients, ATRA plus chemotherapy is, however, still the standard treatment.[13]

Methodology

The retrospective study was carried out at PIMS, Medical Oncology, in Islamabad, Pakistan. A total of 334 patients diagnosed with AML met the inclusion criteria of the study. Among these patients, 191 were males and 143 were females with a minimum age of 12 years and the maximum of 82 years, from 2004 onwards. The overall mean and median age was 31.69 and 30 respectively.

The study was approved by the institutional review board and hospitals ethics committee. The details that might disclose the identity of patients were omitted. Data including age, gender, address, blood counts, blasts percentage, flow cytometry, gene markers, treatment and outcome was evaluated. Age was further categorized into subgroups i.e. 12-18 years, 19-40 years, 41-60 years and above 60 years. Diagnosis of AML was made on bone marrow aspiration and trephine biopsy in all the patients.

Flow cytometry and immunophenotyping was performed in majority of the cases. Biochemical and coagulation profile, Hepatitis B & C serology and echocardiography was done in all the patients. During induction therapy patients received 7 days Arabinoside - cytarabine 200mg/m^2 infusional regime and daunoblastina 60mg/m^2 for 3 days (D3 A7). Bone marrow biopsy was performed on day 28 in majority of patients. Complete remission was defined as blasts less than 5%, absence of extramedullary disease, absolute neutrophil count more than 1000 and platelet count more than 100,000. Partial remission was defined as bone marrow blasts 5-19% and refractory disease meant more than 20%. Treatment related mortality (TRM) was defined as any death within 3 weeks after induction chemotherapy.

Results

The highest number of cases 193(57.8%) were observed in the age group of (19-40 years) followed by 60(20.1%) in the age group of (12-18years), 58(17.4%) in (41-60y) and the lowest were 16(4.8%) in patients greater than 60 years of age. Out of the total of 334 cases reviewed 260(77.8%) patients were diagnosed as AML, 72(21.6%) with APML and 02 (0.6%) as MPD transformed to AML.(Figure 1)

Among these cases 191(57.2%) were males and 143(42.8) were females, with the male to female ratio of 1.335:1.

Out of 334 patients, 150(44.7%) were from Punjab province, followed by AJK and KPK with 75(22.5%) and 68(20.4%) respectively. Among all 334 patients 252(75.4%) had more than 20%, 58(17.4%) had 6-19% and 20(6%) had less than 5% blasts in peripheral blood. Flow cytometry report of 124(37.1%) patients was available which showed, positive results of 110(88.7%) and 14(11.3%) in AML and APML respectively. (Figure 2)

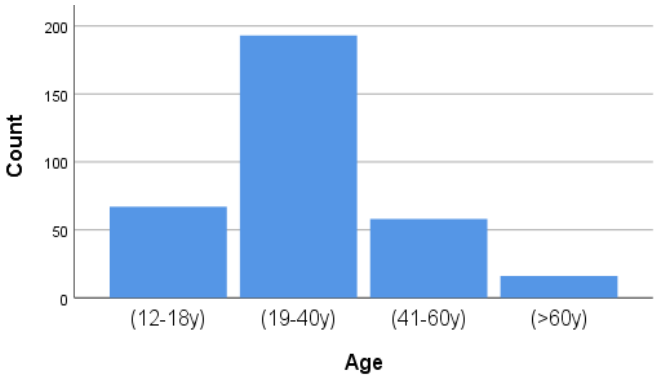

Figure 1. Age distribution

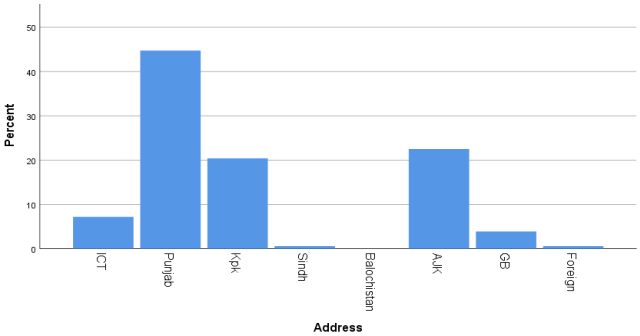

Figure 2. Demographic distribution

Cytogenetic reports of only 35(10.5%) patients were available, that showed normal cytogenetics in 30 (85.7%) and 5(14.3%) showed some abnormality. The available data showed that FLT3-ITD was performed in 30 (9%) patients and it was negative in all patients. NPM1 was performed in 22 (6.58%) patients and only 3 (13.63%) patients were positive. AML-ETO was performed on 32(9.6%) patients and 10(31.25%) were positive. PML-RAR alpha was done in 66 (19.8%) patients and positive was in 35(53.03%).

Hepatitis B surface antigen and anti HCV antibodies were performed at the start of induction in 170(50.6%) of the patients. The positivity of HBsAg and antiHCV antibodies were 7(4.1%) and 6(3.52%) respectively.

"7+3" chemotherapy was given in patients with AML, ATRA/ATO in patients with low-risk APML and chemotherapy + ATRA in the high-risk group of APML. 227 patients (68%) were discharged, among them, Complete remission was observed in 184(81.05%) of cases, 20(8.81%) in partial remission and 25(11.01%) showed refractory disease.

A total of 93 patients died during induction resulting in an (TRM) mortality of 27.3%, whereas 9(2.7%) left against medical advice.

Discussion

Acute myeloid leukemia is an aggressive neoplasm of precursor stem cells of myeloid lineage. The genetic variation results in neoplastic changes and clonal proliferation.[14] This study has elaborated demographics and hematological markers in our population.

AML is generally considered disease of old age with median age of onset around 70 years. In our study, the median age was 30. Previous publications from Pakistan also revealed comparable age at presentation. Similarly, an Indian national study found that the average age of AML patients at the time of diagnosis was 32 years.[15] Perhaps this disparity is due to marked differences on geographical and genetic makeup between different regions. AML is slightly more common in males that is consistent with other studies in region. Majority of patients were from Punjab followed by KPK and AJK as illustrated in previous studies.[16]

Remission induction is the most challenging part of acute myeloid leukemia treatment, associated with high morbidity and mortality. Research and better health care facilities have significantly improved outcome in developed countries, with treatment related mortality less than 5%. The challenges for treatment in resource limited settings are varied including socioeconomic factors, delayed presentation, higher disease burden, resistant infections and lack of intensive care facilities. These factors led to higher treatment related mortality in third world countries. Over the years, the outcome of AML patients has improved because of subgroup risk directed therapies. Due to non-availability of gene markers and cytogenetics in our study, categorization in various groups is not possible. The poor socio-economic status of majority of the patients, the lack of health insurance policies and non availability of targeted therapies are important factors in the poor outcome of acute myeloid leukemia.

TRM is approximately <5% in clinical trials. However, the real-world scenario is different, especially in developing countries. The treatment related mortality in our study was 27.3%, whereas it was 17.8% and 26% in two different studies.[17, 18] Complete remission in our study is 81.05%, it was 71% in another resource-limited setup.[17, 18]

Knowledge of the pre-treatment mutation status of various genes has improved the ability to assign initial treatment. Several new drugs have been approved by FDA and these agents are widely available for newly diagnosed or relapsed patients. For most treatment-naive patients, it is now evident that standard 7+3 represents, under treatment, addition of these targeted agents results in better response and improved survival.[19] Limitation: Our study is a single institution based and may not be able to depict the overall situation in our country.

Conclusion

Acute myeloid leukemia in Pakistani population is seen in relatively younger age group with male predominance.

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