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ORIGINAL ARTICLE

Correlation of Sokal Scoring System with Molecular Response in patients of CML Taking CML Specific Tyrosine Kinase Inhibitors

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ABSTRACT

Background: Chronic myeloid leukemia (CML) is a clonal myelo-proliferative disorder of a pluripotent stem cell.
Aim: To find the frequency of low, intermediate and high risk category in patients of chronic myeloid leukemia and to compare frequency of complete molecular response.
Study design: Descriptive case series**.**
Methodology: Present study was conducted at Hematology Department, Sheikh Zayed Hospital Lahore. 260 patients fulfilled the selection criteria were selected. Sokal score was calculated. Low risk, intermediate and high risk category was assessed. Patients were followed up for 3 months. BCR-ABL translocation detection was done after 3months of treatment and complete molecular response was recorded. All this information was recorded on proforma. Data was analyzed using SPSS version 20. The chi-square test was used to compare the groups. A p-value of 0.05 was considered significant.
Results: The mean age of patients was 49.18±20.33years. There were 144(55.4%) males and 116(44.6%) females. The mean duration of CML diagnosis was 3.52±1.69months. At baseline, 172 (66.2%) had low risk, 76(29.2%) had intermediate risk and 12 (4.6%) had high risk. In the study, complete molecular response was observed in 0% patients.
Conclusion: It was concluded that there is regression in grades of Sokal score in patients of Chronic myeloid leukemia after 3 months treatment with TKIs but there is no complete molecular response observed in any patient after 3 months of treatment with TKIs.
Keywords: Chronic Myeloid Leukemia, Low, Intermediate, High Risk and Sokal Score.

INTRODUCTION

Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder of a pluripotent stem cell1 first described by John Hughes Bennett[1]. CML's cause is uncertain. However it has been linked to tyrosine kinase activity & genetic translocation of the Philadelphia (Ph) chromosome, which contains a disease-causing fusion gene. CML can be identified in three stages: chronic-phase (CP-CML), accelerated-phase (AP-CML) and blast-phase (Blast-CML). However, CP-CML affects over 90% of patients. Over half of all cases of CP-CML are asymptomatic; nonetheless, if left untreated, these patients will proceed to blast-phase CML around 3-5 yrs[2-4].

Imatinib mesylate is a selective Bcr-Abl protein tyrosine kinase inhibitor against cabl, bcr/abl, c-kit, and platelet-derived growth factor receptor (PDGF-R).

Imatinib mesylate has shown to be effective in all stages of CML with a positive Philadelphia chromosome (Ph)[5]. The first BCR-ABL-targeting drug, imatinib mesylate, was approved for the treatment of CML[6]. The introduction of TKIs into CML therapy has a significant impact on the outcome. However, developed prognostic scores during the chemotherapy and interferon era are still used to assess the prognosis of CML patients[7].

For risk stratification of CML patients, prognostic scoring methods have been1developed. Three prognostic approaches are currently frequently used in clinical practice: Hasford & European Treatment Outcome Study (EUTOS)[7,8]. One of the most common types of leukaemia is CML. Patients with CML are generally risk stratified based on a variety of prognostic markers. The Sokal score system is widely used as a prognostic predictor of survival in chemotherapy patients[9].

One study has showed that 68.3% of patients had Sokal score less than 0.8 that means they were in low group, intermediate risk was observed in 27.3% & 4.4% were high risk (Sokal score greater than 1.2) at time of initial presentation. Patients were followed-up and it was noticed that in cases with Sokal score low, in the low risk group, full hematologic response was reported in 86 percent of cases, 86.5% of intermediate and 83.3% of high risk group. But complete cytogenetic response was observed in 58.2% of low risk group, 35.1% of intermediate risk group and 16% (1 case only) of high risk group had complete cytogenic response[10].

The objective of the study was to find the frequency of low, intermediate and high risk category in patients of chronic myeloid leukemia and to compare frequency of complete molecular response.

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METHODOLOGY

This descriptive cross sectional study was conducted on Hematology Department, Sheikh Zayed & Jinnah Hospital, Lahore after IRB permission. Sample size of 260 cases was calculated with 5% level of significance, 2.5% margin of error by taking expected percentage of high risk i.e. Sokal score >1.2 i.e. 4.4% in patients of CML at presentation and after taking TKI therapy. Patients of age 15 – 85 years of either gender with diagnosis of CML (Leucocytosis with peripheral blast cells counts < 5% & hypercellularity of the bone marrow in the presence of blast cells <10% of bone marrow nucleated cells) and BCR-ABL positivity and on quantitative reverse transcriptase polymerase chain reaction (QPCR) and were prescribed TKI therapy.

Patients on treatment with drug other than CML specific TKI (medical record), patients with blast phase of CML and those who received cytotoxic treatment previously (on medical record) were excluded. Demographic information was also obtained. Blood sample from each patient was obtained by using 3cc disposable syringe under aseptic measures and transferred in vials containing EDTA solution. All samples were tested on sysmex Kx21 Haematology Analyzer for platelet count and by observing Giemsa stained peripheral smear for blast count. Abdominal ultrasound was done to measure spleen size. Sokal score was calculated using this information (age, platelet, spleen size and blast cell

count). Low risk, intermediate and high risk category was assessed. Patients were followed up for 3 months. BCR-ABL translocation detection was done by quantitative reverse transcriptase polymerase chain reaction (QPCR) after 3 months of treatment. BCR-ABL status and complete molecular response were recorded as per operational definitions. All this information was recorded.

Statistical analysis: All data was analyzed through SPSS version 20.0. Age and duration of CML were presented as mean & SD. Gender, grade of Sokal score (i.e. low, intermediate and high risk) & absence or presence of complete molecular response were calculated as percentage & frequency. The chi-square test was used to compare the groups. A p-value of 0.05 was considered significant. To control for effect modifiers, data was stratified by age, gender, and CML duration.

RESULTS

Total 260 patients were enrolled. The patients mean age was 49.18±20.33 year. The mean duration of CML diagnosis was 3.52±1.69months as shown in Table-1.

Table-1: Parameter Of All Subjects (n=260)

Variables	Groups	Frequency	%age
Gender	Male	144	55.38
	Female	116	44.62
Age (years)	Mean + SD	49.18 + 20.33	
CML diagnosis (months)	Mean + SD	3.52±1.69	

Patients clinicohematologic feature (age, platelet, spleen size and blast cell count) were taken in account and Sokal score was calculated for each patient. At baseline, 172 patients (66.2%) had low risk, 76(29.2%) had intermediate risk and 12(4.6%) had high risk. All these patients started taking TKI. Sokal score was again calculated at 3 months. At 3 months, 180 patients (69.2%) had low risk, 75(28.9%) had intermediate risk and 5(1.9%) had high risk as shown in Table-2.

Table-2: Sokal score of subjects (n=260)

Variables	Groups	Frequency	%age
Sokal Baseline	Low	172	66.15
	Intermediate	76	29.23
	High	12	4.62
Sokal at 3months	Low	180	69.23
	Intermediate	75	28.83
	High	05	1.92

Out of 172 patients low risk patients at baseline, all had low risk disease after 3 months of treatment. Out of 76 intermediate risk score at baseline, 8 become low risk while 68 persisted intermediate risk group. Out of 12 patient of high risk at baseline, 7 patients become intermediate risk while 5 persisted high risk group after 3 months of treatment. The difference was significant ($p<0.05$) as shown in Table-3.

Table-3: Comparison of Sokal score at baseline and after 3 months

Categories after treatment	At baseline		
	Low	Intermediate	High
Low	172 (100%)	8(10.5%)	0 (0.0%)
Intermediate	0 (0.0%)	68(89.5%)	7(58.3%)
High	0 (0.0%)	0(0.0%)	5(41.7%)

P value 0.000* *Statistically significant

Complete molecular response was observed in 0(0%) patients while 260(100%) did not achieve complete molecular response. In patients with low risk at baseline, no had complete molecular response. In patients with intermediate risk at baseline, no had complete molecular response. In patients with high risk at baseline, no had complete molecular response. Data was stratified for age of patients. Among patients aged 15-30years, patients at low risk, intermediate risk and at high risk, no patient had complete molecular response. Among patients aged 31-60years, at low risk intermediate risk and at high risk, no patient had complete molecular response. Among patients aged 61-80years, in patients at low risk, intermediate risk, and at high risk, no patient had complete molecular response. Among patients with duration 1-3months, in patients at low risk, no patient had complete molecular response. In patients at intermediate risk, no patient had complete molecular response. In patients at high risk, no patient had complete molecular response. Among patients with duration 4-6months, in patients at low risk, no patient had complete molecular response. In patients at intermediate risk, no patient had complete molecular response. In patients at high risk, no patient had complete molecular response as shown in Table-4.

Table-4: Comparison of complete molecular response in Sokal risk score

Age (years)	Complete molecular response	Sokal baseline		
		Low	Intermediate	High
15-30	Yes	0 (0%)	0 (0%)	0 (0%)
	No	38 (100%)	21 (100%)	3 (100%)
31-60	Yes	0 (0%)	0 (0%)	0 (0%)
	No	79 (100%)	33 (100%)	2 (100%)
61-80	Yes	0 (0%)	0 (0%)	0 (0%)
	No	55 (100%)	22 (100%)	7 (100%)
Gender				
Male	Yes	0 (0%)	0 (0%)	0 (0%)
	No	92(100%)	45 (100%)	7(100%)
Female	Yes	0(0%)	0(0%)	0(0%)
	No	80(100%)	31(100%)	5(100%)
Duration of Diagnosis				
1-3 (months)	Yes	0 (0%)	0 (0%)	0 (0%)
	No	81 (100%)	41 (100%)	6 (100%)
4-6 (months)	Yes	0 (0%)	0 (0%)	0 (0%)
	No	91 (100%)	35 (100%)	6 (100%)

DISCUSSION

CML is a myeloproliferative condition that manifests itself in three stages. Early chronic stage disease has the best prognosis, whereas advanced accelerated phase and blast stage disease have worse prognoses with conventional therapy[11].

Over the years, several researchers have attempted to create predictive and prognostic models to risk stratify CML-CR at baseline using a variety of treatment regimens and patient demographics, as well as a variety of statistical tests & endpoints. With very few data from Asian population, it's still unclear which score will proper predict response to current TKI therapy & prognosticate survival outcome among the several available[12-14].

TKIs are being used more frequently to treat CM.[7] TKIs have significantly improved the prognosis of CML patients, After 6–7 years, imatinib-responsive CML patients are expected to have a survival rate of around 100%[15,16].

In our study, the mean age of patients was 49.18±20.33 years. There were 144(55.4%) males and 116(44.6%) females. The mean duration of CML diagnosis was 3.52±1.69 months. Usman et al studied 136 patients, 86 males and 50 female. Median age of their patients was 33 years[9].Kuan and Michael studied 79 patients in a study on epidemiology of CML, 58 were male & 21 were female and median age was 40 years[17].

In our study at baseline, 172 patients (66.2%) had low risk, 76(29.2%) had intermediate risk and 12(4.6%) had high risk according to Sokal score. Somarnam et al assessed Sokal criteria in their patients, 5% patients were in low risk group, Approximately 50% of people were determined to be in the intermediate risk group, while 44% were in high risk group[18]. But Koffi et al reported that among CML patients, 16.6% of patients had low Sokal risk, intermediate risk was observed in 44.5% and 38.9% were high risk at baseline[17].

Usman et al published that 68.3% of patients had low Sokal risk, intermediate risk was observed in 27.3% and 4.4% were high risk at time of initial presentation. Patients were followed-up for 5 years and in low risk group, full hematologic response was

reported in 86 percent of cases, 86.5% of intermediate and 83.3% of high risk group[15].

Another study was conducted by Pavkovic M et al in 2015 in University Clinic for Haematology, Macedonia. In his study 53 patients of CML were treated with TKIs for median duration of 3 years. Out of 53 patients 13(24.5%) patients achieved complete molecular response[19].

Our study was conducted for a duration of 3 month from diagnosis, patient were followed up for 3 months while on treatment with TKIs. Although complete molecular response was not observed in any patient but patients in higher group of Sokal score shifted to lower and intermediate risk groups after treatment with TKIs for 3 month.

Limitations: Our study had limitations like financial constraints, lack of resources, short duration of study and lack of genetic workup.

CONCLUSION

It was concluded that there is regression in grades of Sokal score in patients of Chronic myeloid leukemia after 3 months treatment with TKIs but there is no complete molecular response observed in any patient after 3 months of treatment with TKIs. Hence, longer duration of treatment with TKIs is required and reassessment for molecular response after every year upto 3 years should be done. A follow up of 3 months is too short to achieve a molecular response.

Authors's Contribution: AS&AN: Conceptualized the study, analyzed the data, and formulated the initial draft, **HMM&AA:** Contributed to the proof reading, **AI, AH&TL:** Collected data.

Conflict of Interest: None to declare

Financial Disclosure: None

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