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Sokal & EUTOS Prognostic Scores are not Predictive for Clinical Outcome in Patients with Chronic Phase Chronic Myeloid Leukemia Treated with Imatinib

Namrata Bhutani[1], Deepika Arora[2], Neha Bhutani[3]

[1]Department of Biochemistry, Vardhaman Mahavir Medical College & Safdarjung Hospital, New Delhi.
[2]Department of Anaesthesia, Royal London Hospital, NHS Barts Health, London, United Kingdom
[3]ESIC Dental College, Rohini, New Delhi

Corresponding Author: Neha Bhutani

ABSTRACT

Introduction: Chronic myeloid leukemia (CML) is a malignant myeloproliferative clonal disorder of hematopoietic stem cells. The response to Imatinib can be assessed by criteria given by European Leukemia Net (ELN 2013). CML prognostic scoring systems stratify patients into risk groups based on patient and disease related characteristics at diagnosis. (Sokal, EUTOS).

Methodology: Pre-treatment prognostic scores (Sokal score, EUTOS score) were calculated on the basis of spleen size, platelet count& DLC. After initiation of imatinib therapy, hematological response was monitored at regular intervals &molecular response (BCR-ABL1/ABL1 ratio) assessed after 6 or 12 months.

Results: Cases were divided into two groups, high risk (n=27) & low risk (n=3), based on EUTOS score. 24(88.88%) patients with low risk achieved CHR by the end of 3 months, whereas 2(66.66%) with high risk had it (p=0.3596). An optimal molecular response was seen in 50% of both low risk (n=1) & high risk (n=7) patients based on Sokal score.

Conclusions: In this study, both Sokal and EUTOS score were not predictive for haematological and molecular response in CML patients in chronic phase treated with Imatinib and seem to be inadequate. Better prognostic models need to be suggested for TKI therapy.

Keywords: CML, imatinib, prognostic scores

INTRODUCTION

Chronic myeloid leukemia (CML) is a malignant myeloproliferative clonal disorder of hematopoietic stem cells.[1] It results from a translocation between chromosomes 9 and 22 t(9;22)(q34;q11) which generates the shortened chromosome 22 known as the Philadelphia (Ph) chromosome and the new fusion oncogene, called as BCR-ABL. This oncogene encodes a chimeric 210 kD Bcr-Abl protein that incorporates an activated Abl tyrosine kinase domain.

CML prognostic scoring systems stratify patients into risk groups based on patient and disease related characteristics at diagnosis[5]. The table below mentions two of these prognostic score.[1]

TABLE 1 . Table showing calculation of SOKAL and EUTOS score.

SCORE	CALCULATION	RISK DEFINITION BY CALCULATION
SOKAL	Exp[0.0116*(age-43.4)]+(0.0345*spleen size7.51)+[0.188*(platelet /700)^2)-0.563]+[0.087*(blasts-2.10)]	Low risk < 0.8 Intermediate risk : 0.8-1.2 High risk : > 1.2
EUTOS (European Treatment and Outcome Study)	Spleen*4+ basophils*7	Low risk ≤87 High risk >87

TABLE 2. Table showing criteria for hematological response

Complete Hematologic Response (CHR)	Platelets < 450 x10^9/L, AND White cells < 10 x10^9/L, AND No circulating immature myeloid cells, AND < 5% basophils on differential, AND No palpable splenomegaly

The response to Imatinib can be assessed by criteria given by European Leukemia Net (ELN 2013) as shown in tables below.

TABLE 3 A. Table showing criteria for molecular response

	OPTIMAL	WARNING	FAILURE
6 MONTHS	BCR-ABL1<1%	BCR-ABL1 1-10%	BCR-ABL1 >10%
12 MONTHS	BCR-ABL1 ≤ 0.1 %	BCR-ABL1 >0.1-1%	BCR-ABL1 >1%

TABLE 3 B. Table showing criteria for molecular response

Major Molecular Response (MMR)	BCR-ABL ≤ 0.10%
MR4.0	BCR-ABL < 0.01%
MR4.5	BCR-ABL < 0.0032%
Molecularly undetectable leukemia	BCR-ABL transcripts non-quantifiable and non-detectable

METHODOLOGY

The study was carried out in the Department of Biochemistry in collaboration with the Department of Medicine and Department of Pathology, Maulana Azad Medical College and associated Lok Nayak Hospital, New Delhi. It was a hospital based prospective study.

A sample size of convenience was taken, which included 30 cases of Chronic Myeloid Leukemia (CML) in chronic phase (CP-CML). Newly diagnosed CML patients, in the age group 18-80 years, with diagnosis confirmed by qualitative PCR for BCR-ABL1 fusion gene, who were to be initiated on imatinib therapy. Age and sex matched 30 normal healthy volunteers were taken as controls. Detailed clinical examination and hematological laboratory tests. Pre-treatment prognostic scores (Sokal score, EUTOS score) were calculated on the basis of spleen size, platelet count& DLC. After initiation of imatinib therapy, hematological response was monitored at regular intervals &molecular response (BCR-ABL1/ABL1 ratio) assessed after 6 or 12 months.

RESULTS

Cases were divided into two groups, high risk (n=27) & low risk (n=3), based on EUTOS score. 24(88.88%) patients with low risk achieved CHR by the end of 3 months, whereas 2(66.66%) with high risk had it (p=0.3596). Time to CHR was insignificantly higher in high risk patients as compared to low risk group (p=0.711).An optimal molecular response was seen in 55.55% low risk patients (n=15) &66.66 % (n=2) patients with high risk. In low risk group, 18.51% patients had treatment failure (n=5) while 33.33% (n=1) high risk patients had it.(p=0.765). Cases were divided into three groups, high risk (n=14), intermediate risk (n= 14) & low risk (n=2), based on Sokal score. All patients (100%) with low risk achieved CHR by the end of 3 months, whereas 12(85.71%) with high risk achieved it(p=0.0786). Time to CHR was highest in intermediate risk patients. (p=0.336) An optimal molecular response was seen in 50% of both low risk (n=1) & high risk (n=7) patients. In low risk group 50%patients had treatment failure (n=1) while 7.14%(n=1) high risk patients had it.(p=0.127)

Table 4. CORRELATION BETWEEN SOKAL AND EUTOS SCORES AND RESPONSE TO IMATINIB

RISK CATEGORY	N(%)	MOLECULAR RESPONSE			P-value	HEMATOLOGICAL RESPONSE		P-value
		Optimal	Warning	Failure		CHR at 3 months present, n	CHR at 3 months absent , n	
SOKAL SCORE								
Low risk(%)	2(6.66 %)	1(50)	0	1(50)	*p=0.12*	2(100)	0(0)	*p=0.07*
Intermediate risk(%)	14 (46.66 %)	9(64.28)	1(7.14)	4(28.57)		12(85.71)	2(12.24)	
High risk(%)	14(46.66 %)	7(50)	6(42.85)	1(7.14)		12(85.71)	2(12.24)	
EUTOS SCORE								
Low risk(%)	27 (90%)	15(55.55)	7(25.9)	5(18.51)	p=0.35.	24(88.88)	3(11.11)	p=0.76
High risk(%)	3 (10 %)	2(66.66)	0	1(33.33)		2(66.66)	1(33.33)	

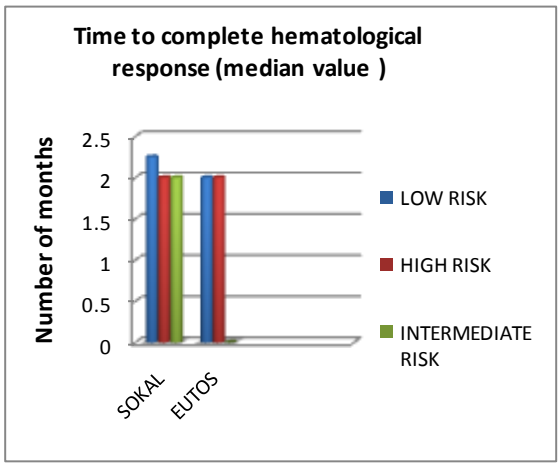

FIGURE 1: BAR GRAPH SHOWING TIME TO COMPLETE HEMATOLOGICAL RESPONSE

DISCUSSION

Many attempts have been made to better suggest a reliable prognostic score for CML-CP over the years.(Table 5)[2,3,4]. While in most of the studies, EUTOS score remained most accurate for predicting the prognosis of CML, two studies from UK and Japan concluded that EUTOS has inadequate efficacy as a prognostic marker.[5,6,7] However, these studies, had a relatively small number of cases. Another study by Kantarjian et al[8] showed superiority of EUTOS score in imatinib treated European population, similar results were found in another study in Chinese population[9].

In this study we found that both Sokal score and Euro score could not significantly differentiate between low and intermediate risk or high risk groups when predicting molecular or hematological response Oyekunle[15] et al suggested that predictive efficacy for PFS remained poor for Sokal score Another study from China[10] on the other hand had the limitation of inability to differentiate low and intermediate risk groups reflected in prediction of OS, not PFS

Ganguly S et al[11] found that EUTOS is better than Sokal score in predicting the outcome of patients of CML treated with imatinib. Although, the EUTOS score appears to outperform as a prognostic model compared to the Sokal and Euro scores in Indian patients in this imatinib era[12,13,14], in most of the studies[16,17,18], our study could not confirm these findings.

Table 5. Table showing results of previous studies done to study predictive efficacy of SOKAL and EUTOS scores.

STUDY	FINDINGS
Marin et al (UK)	EUTOS not predictive of MMR. Sokal has predictive efficacy.
Yamamoto et al (Japan)	EUTOS not predictive of MMR. Sokal and Euro have predictive efficacy.
Hasford et al (Europe)	EUTOS better predictive of response. Sokal or Euro do not have predictive efficacy
Tao et al (China)	EUTOS better predictor of response. Sokal unable to differentiate intermediate Vs high risk.
Kuntegowdanahalli LC et al (India)	EUTOS, Sokal scores predictive of cumulative incidence of MMR
Ganta RR et al (India)	None of the scoring systems predicted the response and outcome effectively in children with CML CP on front line Imatinib.
Ganguly S et al (India)	EUTOS is better than Sokal score in predicting the outcome of patients of CML treated with imatinib.

CONCLUSIONS

In this study, both Sokal and EUTOS score were not predictive for haematological and molecular response in CML patients in chronic phase treated with Imatinib and seem to be inadequate. Better prognostic models need to be suggested for TKI therapy.

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