



Performance of the EUTOS and Sokal Prognostic Scales, To Predict Optimal Response after 6 Months of Imatinib Treatment in Patients with Chronic Myeloid Leukemia in Chronic Phase

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Abstract

Objective: To evaluate and compare the performance of the EUTOS and Sokal prognostic scales, to predict failure to obtain cytogenetic response at 6 months, in patients with Chronic Myeloid Leukemia in chronic phase treated with imatinib, from the Hematology department of the XXI Century National Medical Center.

Material and Methods: The study included 133 adult patients, diagnosed with Chronic Myeloid Leukemia (CML) between January-2006 and July-2018. They received treatment with Imatinib and the Sokal and EUTOS scale were applied and a Complete Cytogenetic Response (CCyR) was evaluated at 6 months of treatment, to know if any of these scales had better performance.

Results: With the Sokal scale, the distribution was 36.8% low risk, 42.9% intermediate risk, and 20.3% high risk. With the EUTOS scale, 68.4% low risk and 31.6% high risk.

59.3% of patients with high risk of Sokal did not achieve CCyR at 6 months and 52.4% of patients with high risk of EUTOS, so the Sokal scale identifies a greater proportion of high-risk patients who will not achieve CCyR at 6 months. However, the difference was not statistically significant ($p=0.072$). In the graphic representation of the ROC Curve (at 6 months of treatment), it is observed that both prognostic scales have very similar discrimination power and the area under the curve was statistically significant. For the case of Sokal (area 0.646, $p=0.005$, CI 95% 0.546- 0.747) and for EUTOS (area 0.726, $p=0.000$, CI 95% 0.639-0.818).

Conclusion: Both scales (Sokal and EUTOS) help us to discriminate between patients who achieved CCyR at 6 months and those who did not obtain this response.

Keywords: Sokal score; Eutos score; Chronic myeloid leukemia; Complete cytogenetic response

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Introduction

Chronic Myeloid Leukemia (CML) is a myeloproliferative disorder, characterized by the expansion of a clone of hematopoietic cells that present the Philadelphia Chromosome (CrPh) [1].

Its annual incidence is approximately 1 to 2 cases per 100,000 people. It represents approximately 15% of all leukemia's in the Western world and has a median age at presentation of 45 to 55 years [2]. The incidence in Mexico is unknown.

After the initial descriptions of CML, which are more than 150 years old, there was minimal progress in its treatment for more than a century. The treatment based on radiotherapy and Busulfan, contributed more to improve the quality of life and not to prolong survival. The improvement in survival was obtained with hydroxyurea, allogeneic hematopoietic stem cell transplantation and subsequently in a minority of patients with Interferon alfa [3].

However, the knowledge of the pathogenesis of the disease led to the discovery of compounds directed against the proteins encoded by BCR-ABL, which inhibit tyrosine kinase activity and therefore nullify the signals that control the leukemic phenotype [4].

For the past two decades, imatinib has been the gold standard for patients with CML P+, as studies established safety and demonstrated its ability to induce high rates of hematological and cytogenetic responses [5].

The response to Tyrosine Kinase Inhibitors (TKIs) is the most important prognostic factor in CML. Responses are defined as "optimal" or "failure". Between optimal and failure, there is an intermediate zone which was previously named suboptimal and is now designated as "warning" [6].

According to the latest guidelines of the European LeukemiaNet 2020 (ELN 2020), an optimal response at 6 months is defined as a BCR-ABL by PCR on an International Scale (IS) <1%, which corresponds to a Complete Cytogenetic Response (CCyR), that is, 0% CrPh in a karyotype and a BCR-ABL>10% IS is defined as failure [7].

The evaluation of risk factors to identify those patients who at diagnosis may have a favorable or unfavorable prognosis has been attempted to be measured by analysis of multiple variables at the initial presentation. The currently accepted prognostic scores in the CML are the Sokal, Hasford, and EUTOS scores. These scores are calculated based on the combination of clinical and laboratory characteristics at the time of CML diagnosis.

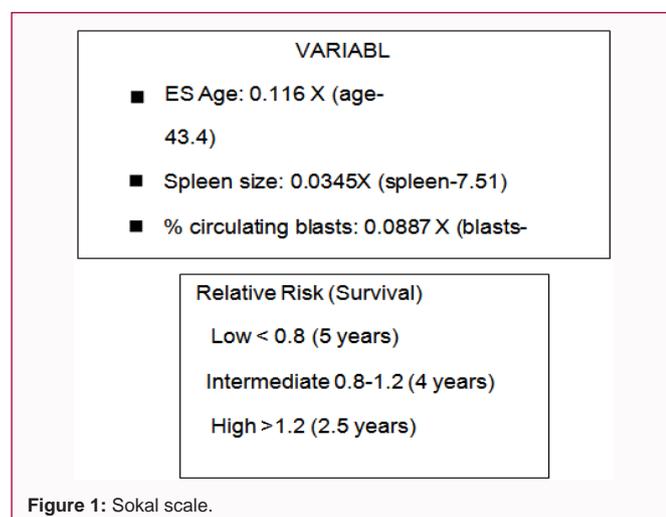
The Sokal score was created in 1984 for chemotherapy treatment, the Hasford score in 1998 for interferon alpha treatment, and the EUTOS score in 2011 for patients treated with imatinib. Thus, the Sokal and Hasford scores were established using Overall Survival (OS) as an endpoint, while the EUTOS score used a CCyR at 18 months [8].

Recently, in the ELN 2020 guidelines, the EUTOS Long Term Survival (ELTS) scale is proposed, which is based on the same Sokal variables, but gives a different value to age (ELN 2020) [7].

The most widely used is the Sokal scale, which takes into account 4 clinical variables: Age, spleen size, percentage of blasts, and platelet count, thereby dividing patients into low, intermediate, and high risk [9] (Figure 1).

Obtaining CCyR is associated with a favorable prognosis; early identification during treatment of those high-risk patients who do not achieve CCyR is crucial [10].

The European Leukemia group proposed the EUTOS prognostic



scale, specifically to evaluate patients treated with TKI (imatinib) [11].

This scale takes into account only two variables at diagnosis, (7 X basophils) + (4 X spleen size), where the spleen is measured in centimeters below the costal border and the basophils in percentage. A EUTOS >87 indicates high risk and <87 low risk [11]. Hoffmann in 2013 validated the EUTOS scale, mentioning that it predicts the probability of obtaining CCyR and better Progression Free Survival (PFS) and demonstrates that age is not a prognostic factor for response in patients treated with imatinib [12]. However, there is still no evidence that any of the risk scales is superior [6].

There is no study that directly compares the most widely used scale (Sokal) against that of EUTOS and this was the interest of the present study. The original article on the EUTOS scale showed that 34% of high-risk patients did not achieve CCyR at 18 months [11]. In our cohort, the obtaining of CCyR at 6 months (current definition of optimal response) was evaluated because it is relevant to identify those patients who do not achieve this response with imatinib, to maintain close surveillance in order to identify those who require a change in treatment [8].

Material and Methods

This retrospective cohort included 133 patients from the XXI Century National Medical Center, IMMS, Mexico City, Mexico, older than 18 years, with a corroborated diagnosis of CML in chronic phase, who received imatinib as the first line of treatment at doses of 400 mg/day, between January-2006 to July-2018. The median age was 44 years (18 to 84) and 45.9% were women and 54.1% men.

Scales

The prognostic risk was calculated with the data at diagnosis, in all patients according to the Sokal and EUTOS scales.

Karyotype

Patients who had a follow-up cytogenetic study, with GGT banding technique and with at least 20 evaluable metaphases, at 6 months of treatment with imatinib were included.

Ethical considerations

This research project was carried out based on the ethical standards. The Regulations of the General Health Law on Health Research Matters and with the Declaration of Helsinki of 1975 amended in 1989, the Nuremberg Code (1946) and current international standards of good clinical research practices. The patients received the usual treatment and follow-up, so it did not imply any additional risk.

Statistical analyses

A comparison of the cytogenetic response proportions was made with Pearson's Chi-square test, the cytogenetic response proportions were compared with the McNemar test, and odds ratios with their corresponding 95% confidence intervals were estimated.

Tables and ROC curves were constructed to find out if there was a better cut-off point than the one proposed internationally, and the areas under the ROC curve were compared.

For the secondary endpoints: Overall survival and progression-free survival, Kaplan and Meier product limit survival curves were constructed and compared with a Cox or proportional hazards regression analysis.

The SPSS 25 program (SPSS, Inc. Chicago Ill) was used and all p

values <0.05 were considered significant.

Results

133 patients were included, the median age was 44 years (18 to 84) and 45.9% were women and 54.1 men. The characteristics of the population are described in Table 1.

When we applied the Sokal scale, 36.8% of the patients showed low risk, 42.9% intermediate risk and 20.3% high risk and when applying the EUTOS scale 68.4% of the patients showed low risk and 31.6% high risk (Table 2).

When evaluating CCyR at 6 months of treatment with imatinib, in the group of patients with low risk of Sokal 75.5% obtained this response, in the group of intermediate risk 66.7% and only 40.7% of the group of high risk (X² Pearson = 9.38, p=0.009) (Table 3).

When evaluating the patients with the EUTOS scale at 6 months of treatment, 72.5% of low risk achieved CCyR and 47.6% of patients who had high risk (X² Pearson =7.8, p=0.005) (Table 4).

Therefore, in the evaluated patients, 59.3% of patients with high risk of Sokal did not achieve CyCR at 6 months and 52.4% of patients with high risk of EUTOS, therefore the Sokal scale identifies a greater proportion of high-risk patients who will not achieve CyCR

Table 1: Characteristics of the patients.

Basal characteristics of patients (N=132)	
Age at diagnosis Median (range)	44 (18-84)
Gender	
Women	61 (45.9)
Men	72 (54.1)
Spleen size (cm) Median (range)	5.7 (0-23)
Platelets (x 10 ⁹ /L) Median (range)	599 (43-3471)
Peripheral blood blasts (%) Median (range)	1 (0-10)
Basophils in peripheral blood (%) Median (range)	6 (0-20)
Cytogenetics at diagnosis (% CrPh) Median (range)	96 (30-100)
Cytogenetics at 6 months (% CrPh) Median (range)	22 (0-100)

Table 2: Frequencies according to the Sokal and EUTOS scales.

RISK	SOKAL N (%)	EUTOS N(%)
Low risk	49 (36.8)	91 (68.4)
Intermediate risk	57 (42.9)	
High risk	27 (20.3)	42 (31.6)

Table 3: CCyR percentage at 6 months with Sokal scale.

RISK Sokal	CyCR 6 months N (%)	No CyCR 6 mnyhs N (%)
Low	37 (75.5)	12 (24.5)
Intermediate	38 (66.7)	19 (33.3)
High	11 (40.7)	16 (59.3)
TOTAL	86 (64.7)	47 (35.3)

Pearson's chi square for Sokal scale (p=0.009)

Table 4: CCyR percentage at 6 months with EUTOS scale.

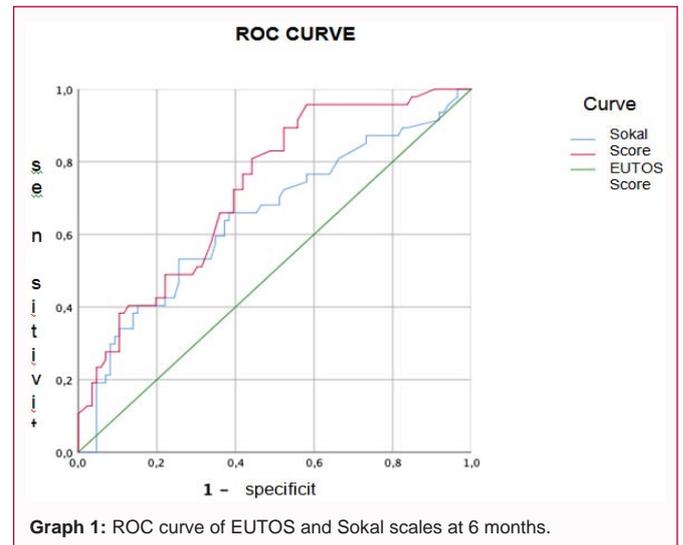
RISK EUTOS	CyCR 6 months N (%)	No CyCR 6 months N (%)
Low	66 (72.5)	25 (27.5)
High	20 (47.6)	22 (52.4)
TOTAL	86 (64.7)	47 (35.3)

Pearson's chi square for Sokal scale (p=0.005)

Table 5: Area under the curve of the EUTOS and Sokal prognostic scales at 6 months.

Contrast result variables	Area	Sig	IC 95%	
			Lower limit	Upper limit
Puntaje de Sokal	0.646	0.005	0.546	0.747
Puntaje EUTOS	0.726	0	0.639	0.818

ROC of EUTOS and Sokal scales at 6 months



at 6 months. Because the two scales were measured in each patient to compare them, the McNemar test was applied, however, no statistically significant difference was found between both scales to identify high-risk patients (p=0.072).

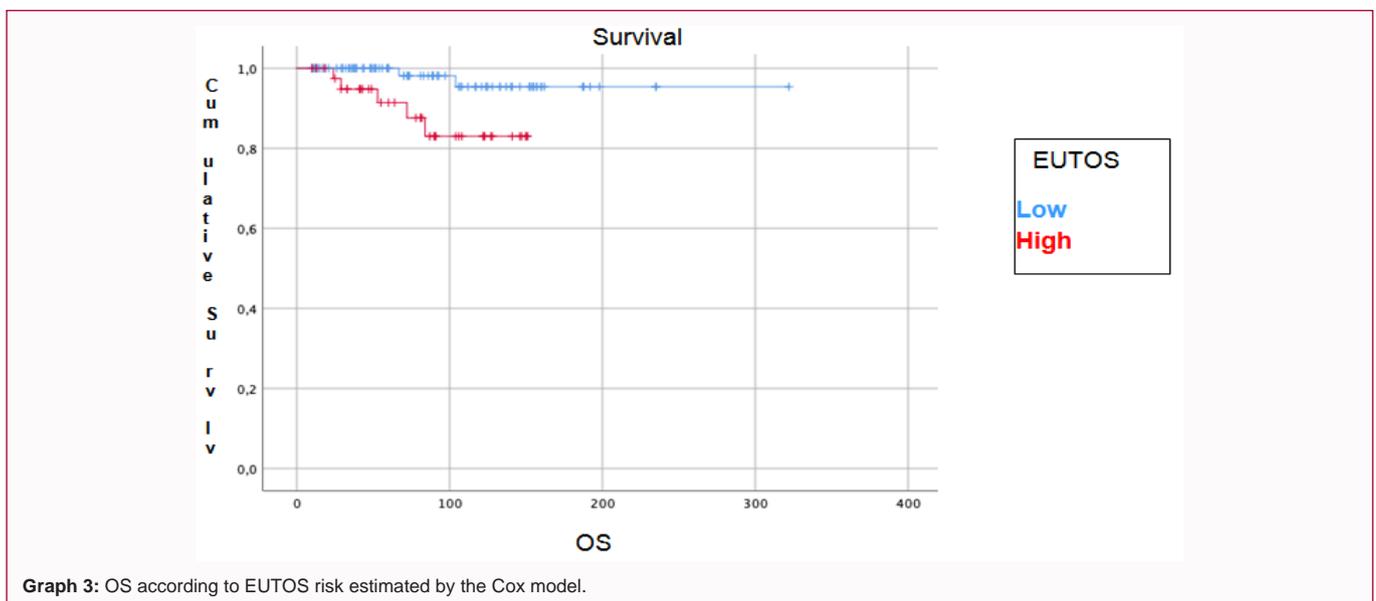
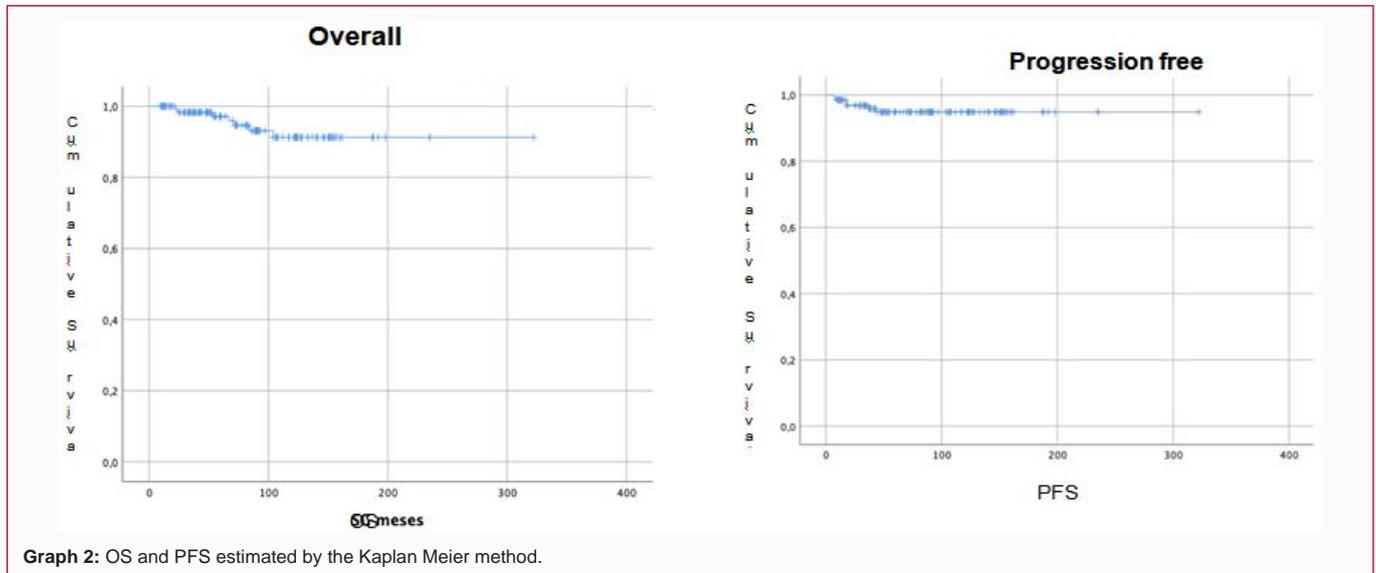
When performing a binary logistic regression, we found that the two scales (EUTOS and Sokal) were statistically significant.

When patients are classified as high risk with either of the two scales, they present an increased risk of not obtaining CCyR at 6 months, however, the risk is higher with Sokal, since it increases the risk 4 times compared to with 3 times with the EUTOS scale.

In the graphic representation of the ROC Curve (at 6 months of treatment), it was observed that both prognostic scales have very similar discrimination power and the area under the curve was statistically significant. For Sokal (area 0.646, p 0.005, CI 95 0.546-0.747) and for EUTOS (area 0.726, p 0.000, CI 95% 0.639-0.818). In other words, the EUTOS scale only correctly identifies 0.08 more patients than the SOKAL scale, therefore both scales help us to discriminate between patients who achieved RCC at 6 months and those who will not obtain this response and the probability that this classification is correct is reliable, being slightly higher with the EUTOS scale, since its area under the curve is greater (Graph 1 and Table 5).

Twelve patients with loss of cytogenetic response were identified, 6 with loss of complete hematological response, 6 with disease progression of which 2 progressed to blast crisis and 4 to accelerated phase. There were 7 deaths, 2 of them died due to progression of the disease to blast crisis. The exact cause of death could not be determined for the rest of the patients.

By constructing Kaplan and Meier product-limit survival curves, a mean OS of 299 months was obtained with an estimate at 84 months



of 91%. A mean PFS of 306 months was obtained with an estimate of 95% at 44 months, without progression of any patient after 44 months (Graph 2).

When developing curves classifying patients by risk group, the Cox model was applied and we obtained statistical significance for OS with the EUTOS scale. ($p=0.022$), with a mean OS for low-risk patients 311 months and high-risk 135 months (Graph 3).

Discussion

The outcome of CML patients in the era of tyrosine kinase inhibitors has changed favorably. Prognostic scales were performed before the advent of these drugs, such as Sokal, which was used during treatment based on chemotherapy and alpha interferon. In the case of the EUTOS scale, it was created in the era of ITK drugs, using only the size of the spleen and basophils as variables. For this reason, this study compared the performance of the Sokal and EUTOS scales.

For both scales, the identification of high-risk patients was higher compared to that reported in the literature. In Jabbour's work carried

out at the MD Anderson Cancer Center, Houston, a high risk of Sokal was reported in 7% of patients and a high risk of EUTOS in 8% [13] and in the case of the study by Rosti, of the group Italian, 14% of patients with high risk of Sokal were reported [14].

The identification of a higher percentage of high-risk patients can be explained by the lack of routine studies in our population, which means that the identification of the disease is delayed, detecting patients when they already present advanced symptoms of the disease.

According to current ELN recommendations, the goal of an optimal response represents the achievement of CCyR at 6 months of TKI treatment, which is associated with the best long-term outcome and survival [7]. For this reason, the assessment of CCyR at 6 months was considered important in our study.

In this study, 133 patients with CML-chronic phase were evaluated, who received first-line treatment with imatinib, of these 59.3% of patients with high risk of Sokal did not achieve CCyR at 6 months and 52.4% of patients with high risk of EUTOS.

When performing the McNemar test to compare the two scales, there was no statistically significant difference to identify high-risk patients ($p=0.072$). Therefore both scales are useful to identify a group of high-risk patients.

However, it is important to note that the difference in the identification of high-risk patients who achieved CCyR at 6 months with the Sokal scale was slightly greater. But on the other hand, if we take into account the number of variables used by each of the scales (EUTOS only includes spleen size and basophil percentage), the application of this scale could be easier in clinical practice.

When analyzing the sensitivity using ROC curves, we observed that both scales help us to reliably discriminate those patients who did not achieve an optimal response.

Contrasting data are reported in the literature, for example, Jabbour at MD Anderson Center, Houston concluded that the EUTOS scale does not predict the outcome in patients with CML in chronic phase [13]. Marín at Hammersmith Hospital, London reports that Sokal is useful for predicting OS, PFS and CCyR and the EUTOS scale fails to predict these outcomes [15] and on the other hand a Spanish study mentions that the high risk of EUTOS identifies patients with an unfavorable outcome [16].

Both scales are capable of identifying cases of poor prognosis. However, the Sokal scale seems to identify a higher proportion of cases with a poor prognosis than the EUTOS scale. The 2 variables that make up the EUTOS scale are also part of the Sokal scale and for this reason we would think that the latter identifies more cases of poor prognosis because it contains more information (greater number of variables).

The prognostic value of basophilia was first established in patients receiving hydroxyurea or interferon- alpha and has more recently been confirmed for patients receiving imatinib or other BCR-ABL inhibitors [17].

Conclusions

1. Both the Sokal scale and the recent EUTOS scale allow us to reliably identify high-risk patients.
2. The Sokal scale, although designed prior to the era of tyrosine kinase inhibitors, continues to be a useful and reliable tool for patients treated with imatinib who are at risk of an unfavorable outcome.
3. Both prognostic scales, Sokal and EUTOS, have very similar discriminatory power, taking into account the obtaining of CCyR at 6 months of treatment, however, the EUTOS scale is slightly higher.
4. In the Mexican population, the percentage of high-risk patients is higher than that reported in the United States and Europe.
5. The risk of EUTOS impacts overall survival.
6. Identifying high-risk patients alerts the doctor for a close and careful follow-up and thus being able to identify treatment failure early and make timely therapeutic decisions, such as switching to a second- generation tyrosine kinase inhibitor.

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