EUTOS score is not predictive for survival and outcome in patients with early chronic phase chronic myeloid leukemia treated with tyrosine kinase inhibitors: a single institution experience

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ABSTRACT

To validate the recently reported EUTOS score, we applied it to 465 patients with early chronic phase chronic myeloid leukemia (CML-CP) treated with standard-dose imatinib (n=71), high-dose imatinib (n=208), or second generation tyrosine kinase inhibitors (2-TKIs; n=186), and assessed its ability to predict event-free survival (EFS), transformation-free survival (TFS), and overall survival (OS). The median follow-up was 69 months. The overall complete cytogenetic response and major molecular response (MMR) rates were 92% and 85%, respectively. The 3-year EFS, TFS, and OS rates were 86%, 95%, and 97%, respectively. Of the 465 patients, 427 (92%) were in low EUTOS score category. There was no difference in the MMR, TFS, EFS, and OS rates between patients with low and high EUTOS score, overall and within specific therapies. In conclusion, 8% of patients with CML-CP treated at our institution are in the high EUTOS score; in this population, the EUTOS score was not predictive for outcome.
Introduction

The introduction of the tyrosine kinase inhibitors (TKIs), which suppress the molecular processes driving chronic myeloid leukemia (CML), has revolutionized the management and prognosis in CML. Imatinib therapy induced high rates of complete cytogenetic (CCyR) and major molecular responses (MMR), and improved survival in CML. Second generation TKIs (dasatinib, nilotinib) are more potent BCR-ABL inhibitors with demonstrated efficacy in patients resistant to or intolerant of imatinib. Dasatinib and nilotinib were first approved for patients resistant to or intolerant of prior imatinib therapy, are active against most BCR-ABL mutations with the exception of T315I, and have well-established safety profiles. Single-arm phase II studies suggested, and phase III randomized trials later confirmed that dasatinib and nilotinib were superior to imatinib, inducing faster and higher rates of CCyR and molecular responses. Therefore both drugs were granted FDA approval as initial therapy for patients with newly diagnosed CML in chronic phase.

Until recently, the prognosis of patients with CML treated with TKI was based on scores developed in the chemotherapy and interferon era. The European Leukemia-Net has developed a new scoring system [European Treatment and Outcome Study (EUTOS) score] using data from 2,060 patients with newly diagnosed CML chronic phase (CML-CP) treated with imatinib-based regimens. The EUTOS score was reported to have superior prognostic power compared with the Sokal score. The EUTOS score using the percentage of basophils and spleen size divided patients in two groups of low- and high-risk patients with significant correlations with the achievement of an 18-month complete cytogenetic response (CCyR) and progression-free survival.

The aims of this study were to validate the EUTOS score in an independent cohort of patients with early CML-CP referred to our institution and treated with TKIs, and to assess its
ability to predict event-free survival (EFS), transformation-free survival (TFS), and overall survival (OS).

**Material and Methods**

Four hundred and sixty-five consecutive patients with newly diagnosed CML-CP were treated with imatinib 400 mg daily (n=71), imatinib 800 mg daily (n=208), and second generation TKIs [2nd TKI; (n=186; dasatinib n=88, nilotinib n=98)] in sequential phase II trials. Entry criteria were similar for all trials. CML-CP was as previously defined. Patients were treated on University of Texas MD Anderson Cancer Center IRB-approved protocols. Informed consent was obtained in accordance with the Declaration of Helsinki. Response criteria were as previously described. Conventional cytogenetic analysis was done in bone marrow cells using G-banding technique. At least 20 metaphases were analyzed and marrow specimens were examined on direct or short-term (24 hours) cultures. Major molecular response (MMR) was defined as a BCR-ABL/ABL transcript ratio of less than or equal to 0.1% (international scale). A complete molecular response was defined as undetectable transcripts with an assay with sensitivity of at least 4.5-log.

The EUTOS score was defined by \((7 \times \text{basophils}) + (4 \times \text{spleen size})\) where the spleen size was measured in centimeters below the costal margin and basophils as a percentage at baseline. A EUTOS score of > 87 indicates high risk and ≤ 87 low risk.

EFS was measured from the start of treatment to the date of any of the following events: death from any cause at any time, loss of complete hematologic response, loss of major cytogenetic response, or progression to accelerated or blast phases. TFS was measured from the start of treatment to the date progression to accelerated or blast phases at any time, last follow-up, or death from any cause. Survival probabilities were estimated by the Kaplan-Meier
method, and compared by the log-rank test. Differences among variables were evaluated by the chi-square test and Mann-Whitney $U$ test for categorical and continuous variables, respectively.

**Results and Discussion**

A total of 465 patients were treated. The median age was 47 years (15 to 85). The median time from diagnosis to TKI therapy was 1 month (0 to 6), with 119 (25%) had received previous cytoreduction therapy. The median follow-up was 117 months (16 to 130) for the patients receiving standard-dose imatinib ($n=71$), 88 months (4 to 118) for those receiving high-dose imatinib ($n=208$), and 30 months (3 to 69) for those receiving 2$^{nd}$ TKI ($n=186$). The median basophils percentage at baseline was 3 (0 to 19) and the median splenomegaly size was 0 cm (0 to 30). Three hundred and nineteen patients (69%), 112 (24%), and 34 (7%) were in low, intermediate, and high-Sokal score category, respectively.

The overall CCyR and MMR rates for the whole study group were 92% and 85%, respectively. The overall CCyR rates were 87%, 91%, and 95%, for patients treated with standard-dose imatinib, high-dose imatinib, and second generation TKIs, respectively. The overall MMR rates were 78%, 86%, and 86%, respectively. The 3-year EFS, TFS, and OS rates for the whole group were 86%, 95%, and 97%, respectively. The 3-year EFS rates were 80%, 85%, and 91%, for patients treated with standard-dose imatinib, high-dose imatinib, and second generation TKIs, respectively. The 3-year TFS rates were 89%, 95%, and 99%, respectively. The 3-year OS rates were 93%, 97%, and 99%, respectively.

Overall, of the 465 patients, 427 [92%; 67 (94%) receiving standard-dose imatinib, 189 (91%) high-dose imatinib, 171 (92%) 2$^{nd}$ TKI] were in low EUTOS score category (Table1). Patients with low EUTOS score had higher rates of CCyR at anytime compared to patients with high EUTOS score (93% versus 81%, $p=0.02$). This difference was mainly significant among
patients receiving 2nd TKIs (p=0.03) while it was not different among patients receiving imatinib (p=0.27). There was no difference in the rates of MMR (85% versus 81%, p=0.48) between patients with low and high EUTOS score. There was no difference in EFS, TFS, and OS rates between patients with low and high EUTOS score, overall and within specific therapies (Figure 1). The lack of difference was consistent whether patients were treated with imatinib or 2nd generation TKI. Similarly, there was no difference in overall outcome when applying the Sokal score (data not shown).

In our study groups, the EUTOS score was not predictive for overall MMR, TFS, EFS, and OS among patients in early chronic phase treated with imatinib and second 2nd TKIs. Using the EUTOS scoring system, the proportion of high-risk patients in our study was similar to that recently reported in 2 studies by Hasford et al18 and Marin et al,20 where the rate of high-risk patients was around 10%. Compared with the previous studies, our analysis has the advantage of assessing, additionally, the impact of the EUTOS score among patients receiving 2nd TKI as frontline therapy. Unlike the report by Hasford et al, but similar to the report by Marin et al, the EUTOS score in our analysis did not predict for outcome of patients. This difference may be in part due to different CML populations and possibly to the size of our study population where in the setting of treatment with high efficacy that potentially may overcome the prognostic impact of the disease burden at baseline, a larger number of patients may be needed in order to show significant difference. In addition, the EUTOS score, like the Sokal score, measures at least in part the disease burden, and may not reflect the dynamic of the disease in response to TKI therapy. New prognostics models reflecting the disease biology and factors affecting response to TKI therapy are being assessed and may help better tailoring of upfront therapy.21

In conclusion, the EUTOS score did not predict for outcome in an independent cohort of patients with early chronic phase treated at our institution with imatinib and 2nd TKIs. New prognostic models are warranted in the modern era of TKI therapy.
Authorship

EJ designed concept, analyzed data, wrote and approved the manuscript. HK and JC designed concept, wrote and approved the manuscript. SOB, AQC, AN, and GGM provided materials and approved the manuscript. SP analyzed data and approved the manuscript.

Acknowledgments

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References:


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### Table 1: EUTOS score and outcome*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Overall N=465</th>
<th>Low EUTOS score 427 (92%)</th>
<th>High EUTOS score 38 (8%)</th>
<th>p-value</th>
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<tr>
<td>CCyR (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Overall (evaluable=454)</td>
<td>92</td>
<td>93</td>
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<td>400 mg</td>
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<td>86</td>
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<td>800 mg</td>
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<td>92</td>
<td>79</td>
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<tr>
<td>MMR (%)</td>
<td></td>
<td></td>
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<tr>
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<td>800 mg</td>
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<tr>
<td>3-year EFS (%)</td>
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CCyR=complete cytogenetic response; MMR=major molecular response; EFS=event-free survival; TFS=transformation-free survival; OS=overall survival; TKI=tyrosine kinase inhibitors

* Sixty-seven patients (94%) receiving standard-dose imatinib, 189 (91%) receiving high-dose imatinib, and 171 (92%) receiving 2nd TKI were in low EUTOS score category
**Figure 1A:** Event-free survival among patients with high and low risk EUTOS score

![Graph showing event-free survival](image)

- **Total Event**
  - Low: 427, 77
  - High: 38, 8

- **p = 0.71**
Figure 1B: Transformation-free survival among patients with high and low risk EUTOS score

- Low: 427, 29
- High: 38, 4

Total Transformation: p = 0.49
Figure 1C: Overall survival among patients with high and low risk EUTOS score
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