Abstract

Since introduction of oral chemotherapy in the treatment of CML there is a continual effort for estimation of prognosis including future response to the therapy. Despite the first efficient prognostic scoring systems were designed for the patients treated with busulfan or hydroxyurea and interferon-alpha, respectively, Sokal and Hasford (Euro) scores are used for the patients treated with tyrosine kinase inhibitors (TKI) nowadays with a very good predictive value. The EUTOS score - specifically designed for the treatment with TKI - is (unlikely the previous scores) very easy to be counted, however, in some cohorts of patients failed to provide optimal predictive role for overall survival of patients. New strategies for CML prognostic score computation include implementation of newly designed statistic tools and end-points. On the other hand there is a simple possibility of designing the combination scores or including the early response to the treatment into the scoring system. However, because of significant role of biological properties of leukemic clones that may not be reflected by the score components the fate of the individual patients may not fit in 100% with their scores. For the further improvement of existing scores value implementation of new biological/molecular markers is clearly needed.

Keywords: Chronic myeloid leukemia; Molecular markers; Chemotherapy; Hematopoietic stem cell transplantation

Commentary

Even today in the era of targeted treatment of Chronic Myeloid Leukemia (CML) with Tyrosine Kinase Inhibitors (TKI) the fate of individual patient is in many cases determined by hematologic progression to accelerated or blastic phase. After the CML transformation response to salvage treatment and survival of most patients are poor. From the clinical point of view it is important that in actual patient it is impossible to accurately predict the time to this transformation. Since the time when meaningful array of treatments for CML became available (oral chemotherapy, interferon alpha and hematopoietic stem cell transplantation) we can observe the efforts of physicians to estimate the patients´ prognosis before the initiation of the treatment using various clinical and laboratory markers. Clearly, these attempts were successful or not depending statistical methods used (mostly Cox multivariate analysis and more recently cause-specific or sub distribution hazard models) and the numbers of patients included into retrospective studies designed for prognostic score estimation. Importantly, in addition to that these groups of patients had to be treated with homogenous treatment able to achieve similar results [1]. The result of this approach is usually the number which value allocates the individual patient to the specific prognostic group (“low”, “intermediate” or “high” risk).

First attempt to design the CML prognostic score based on retrospective evaluation of patients treated at single institution was done by Tura and colleagues in 1981 [2]. Tura´s index is easily counted (Table 1), however, because of limited numbers of patients analyzed it had not proved its value in other cohorts of patients similarly like the prognostic score designed by Cervantes in 1982 [3]. Similarly unsuccessful attempts to design a better scoring system were performed twice by Kantarjian et al. [4,5]. They were based on the retrospective analysis of 303 patients with CML treated by oral chemotherapy agents in Houston from 1965 to 1982 and 406 patients treated predominantly with interferon in years 1975-1986. The advantage of these score was the simplicity of counting, however, their prognostic value was limited because of limited numbers of patients analyzed resulting in less robust results. Therefore, all these above-mentioned prognostic systems were not widely used and have not proved its´ value in other cohorts of patients.

The most successful prognostic scoring system was introduced by Sokal and international group of statisticians and CML experts in 1984 [6]. At that time the largest group of 813 patients treated with oral chemotherapy in six European and American centers was evaluated retrospectively. Sophisticated statistical analysis resulted in complicated equation based on the age, spleen size, platelet count and percentage of blasts in peripheral blood. Sokal score proved its´ value in many studies and has been still recommended for estimation of prognosis in CML patients treated with TKI today by European LeukemiaNet experts´ guidelines [7]. However, it had certain limitations for estimation of prognosis in patients treated with interferon [8] and today has lower power to discriminate between the low and intermediate groups of patients.

With the aim to overcome the lower value of Sokal score for CML patients treated with interferon Hasford et al. from German CML Study Group developed the score based on the retrospective analysis of 490 patients treated with busulfan, hydroxyurea and interferon within German CML 1 prospective study [9]. The computation of this score is less complicated than in the Sokal score case. Interestingly, the score included (unlike other scores) gender and percentage of erythroblasts in peripheral blood as significant variables. This score has not been used many times since its´ development and later was replaced by so called Euro score [8]. Euro score was the result of international project focused on the development of score valid specifically for the
CML patients treated with interferon. In a retrospective analysis 1201 patients were included and designed score was subsequently validated in the second population of 493 patients. This score was later validated and proved in many studies and is also recommended for the practical use presently.

In an attempt to develop a score more suitable for patients treated with TKI large EUTOS project led to design of easy-to-count EUTOS score based on the end-point of achievement of complete cytogenetic response at 18 month of treatment with TKI [10]. This end-point most robustly predicted progression-free survival of TKI-treated patients. Largest cohort of 2060 patients was analyzed and later the score was validated in the second group of more than 1800 patients. Based on the percentage of basophils and spleen size the score discriminated two groups with low and high risk. Several studies have proved EUTOS score value, however other studies have not [11-13]. The main problem is probably the end-point: for optimal treatment response and survival a subgroup of patients can achieve complete cytogenetic response later than at 18 month time-point, however, without compromised survival thanks to the efficient second-line treatment. Actual proportion of these patients may interfere with predictive value of EUTOS score. Are there any ways to bypass other competing end-point and bias and design the better score? Various strategies were proposed: 1/ to use different end-points because more CML patients treated successfully with TKI are dying from different causes than CML. Logically the German group of statisticians analyzed with this aim 1236 patients treated within the German CML Study IV and find out that the best model for prediction of CML-related deaths may be based on age, gender and spleen size [1]; 2/ to combine existing scoring systems with the results of early molecular response (proved to correlate with further response and survival in may trials) [14]; 3/ combination the various existing scores within a new one. The group of Korean scientists recently confirmed different probabilities of achieving complete cytogenetic response at 12 month for the groups of patients with combination of low scores and for the patients who have all three scores (Sokal, Euro and EUTOS) in the high-risk group categories [15]; 4/ to use novel biological or molecular markers that may further improve the prognostication [16,17].

**Conclusion or Do we need Other New Scores?**

Most CML patients treated with TKI have excellent prognosis even while having high-risk score. On the other hand there are the rare patients at low risk who have other risk feature not covered by the scores (for instance additional cytogenetic abnormality). This adverse biological property may cause the early abrupt CML progression into the advanced phase and finally lead to the treatment failure and death. Probably even the best score cannot have 100% true prediction. Anyway, for the generation of new better score discovery of novel biologic or molecular marker may be needed.

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References


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