Comment on "Second-generation tyrosine kinase inhibitors improve the survival of patients with chronic myeloid leukemia in whom imatinib therapy has failed" Haematologica 2011;96(12):1779-82

The added value of 2nd generation tyrosine kinase inhibitors (TKIs) is currently perhaps the most-discussed issue in chronic myeloid leukemia (CML) research and treatment. Therefore, with their recently published article "Second-generation tyrosine kinase inhibitors improve the survival of patients with chronic myeloid leukemia in whom imatinib therapy has failed", Ibrahim *et al.*[1] focussed on an important topic. However, in our opinion, the methodological approach used in this paper is not always appropriate.

The choice of the historical control group treated with interferon-alfa seems not to be optimal. Even before the imatinib era, progress had been made in the treatment of CML as the results of the consecutive German studies and of the French CML-study group show.[2-4] We doubt that the results of the 20-year old MRC trial represent an appropriate comparator group for the results achieved by the use of 2nd generation tyrosine kinase inhibitors. Furthermore, the authors use two different definitions of failure for the two groups: in the imatinib group, failure was defined according to the ELN criteria[5] while in the interferon group it was defined according to the criteria of Marin *et al.*[6] Criteria for failure in the interferon era included much more serious events than in the imatinib era. The lack of comparability due to different failure criteria may have led to a bias in favor of the 2nd generation tyrosine kinase inhibitor-treated patients since they were in better general condition when receiving their second-line treatment.

Our main point of criticism is that the authors compare the two groups with respect to survival from the time of diagnosis instead of survival from the time of treatment failure. From a statistical point of view, this may introduce considerable bias. During the time from diagnosis to failure of first-line treatment, a patient is not at risk of death, since a patient who dies without failure will not be part of the analysis sample. Hence, the time interval between diagnosis and treatment failure (i.e. starting point of the second-line treatment) should not be considered in the comparison as the survival up to this time point cannot be attributed to second-line treatment which would only have been administered later. Unfortunately, the authors did not comment on the management of time to failure. Especially when considering the different definitions of failure, there might be considerable differences between the two treatments.

Let us consider a hypothetical example: two second-line therapies carry the same risk of death, but the times-to-switch to these second-line treatments differ considerably. In this example, it is likely that a significant survival difference is detected between the two patient groups, although the second-line treatments provide the same survival probabilities after they have actually been applied. In fact, what Ibrahim *et al.*[1] primarily compared is not a group of patients with 2nd generation TKI to a group of patients with palliative therapy after treatment failure, but a group of patients receiving imatinib as first-line therapy to a group of patients starting with interferon alpha.

The risk of death may also depend on the time of failure. In this case, it would be adequate to use techniques for left-truncated data. Starting time point would be the date of diagnosis but patients would not enter the risk set until the time of failure. This approach is described in detail by Klein and Moeschberger.[7]

Finally, we would like to point out that, at least for some patients, allogeneic stem cell transplantation (SCT) may have been another option for treatment after failure of the first-line therapy with interferon or imatinib. As the importance of SCT in the treatment of CML has been continuously decreasing in the imatinib era,[8] it can be questioned whether the choice between SCT after imatinib failure and second-generation TKI is comparable to the choice between SCT and palliative therapy 20 years ago. Consequently, both cohorts might be subject to different selection mechanisms. This is a characteristic problem of historical comparisons which can only be avoided within a randomized trial.

However, we agree with the authors that second-line TKIs should be made available to all patients in whom imatinib treatment has failed.

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