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Letter to the Editor

Tyrosine-kinase inhibitor discontinuation in chronic myeloid leukaemia after deep molecular response: a meta-analysis with meta-regression

Melania Rivano, Luca Cancanelli, Andrea Zovi, Chiara Addis, Daniele Mengato, Marco Chiumente and Andrea Messori

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Dear Editor,

Treatment-free remission (TFR) after discontinuation of a tyrosine-kinase inhibitor (TKI) has become an emerging goal for chronic myeloid leukaemia (CML) patients who have achieved a deep and stable response. Discontinuation of TKIs has the potential to reduce the side effects associated with lifelong therapy and can also be a cost-effective intervention. More importantly, in some patients this strategy can be a cure for CML.

In studying the evidence available on TKIs discontinuation in patients with complete molecular remission, Campiotti et al.1 included only studies employing imatinib. In their analysis, the length of follow-up differed across the included studies, and no adjustment was made for this potentially important factor.

In the present study, we extended the analysis of Campiotti et al. by including the more recent studies published on second-generation TKIs and we also investigated the effect of post-discontinuation length of follow up on the risk of molecular relapse. The terms molecular remission and molecular relapse refer to the period when the trials were conducted; other more modern terms (detectable BCR/ABL1) are currently in use.

We carried out a PubMed search (from 1 January 2008 to 31 May 2019) to identify all published studies that reported information on TKIs discontinuation in CML patients with complete molecular remission. The following MeSH terms were used: ‘chronic myeloid leukaemia’, ‘tyrosine kinase inhibitor’, ‘imatinib’, ‘nilotinib’, ‘dasatinib’, ‘discontinuation’. Studies were considered eligible if they were randomised controlled trials (RCTs) published over the past 10 years and reported the clinical outcomes needed for our analysis. Statistical analysis was performed using the OMA (Open-Meta-Analyzer) software (http://www.ceb.m.brown.edu/openmeta/index.html, 2018). The primary endpoint of our analysis was the occurrence of molecular relapse over time after TKI discontinuation.

Our meta-analysis included the 13 studies reported by Campiotti et al.1 and 7 studies on second-generation TKIs.2–6 The EURO-SKI7 and the GELMC8 studies included also patients treated with imatinib, dasatinib, nilotinib or bosutinib. We excluded 2 studies9,10 because the information needed for our analysis was not available. The length of post-discontinuation follow-up represented the covariate for our meta-regression. This follow up ranged from 6 to 94 months in the included studies.

Our results showed that, irrespective of the length of follow-up, approximately 50% of patients experienced a molecular relapse after TKIs discontinuation (crude rate: 861/1915; meta-analytic relapse rate: 46.5%; 95%CI: 40.9% to 52%; Figure 1, Panel A). Limitations of the published trials included the lack of a standardized definition of molecular response as well as some differences in the inclusion criteria.

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Our meta-regression did not find any association between risk of relapse and post-discontinuation follow up (Figure 1, Panel B). Since the relapse rates did not increase with the length of follow-up, this could suggest that the initial characteristics of the disease have a main role in determining whether or not the patients maintain remission after drug discontinuation. Several studies showed that CML molecular relapse occurs mainly during the first 6 months after imatinib discontinuation; however, late molecular relapse can also occur. Other explanations, in keeping with the EURO-SKI analysis, could be that duration of TKI-treatment and duration of deep molecular response prior to stop might have influenced the achievement of a successful TKI-stop. Although several studies have suggested a number of prognostic factors (e.g., age at diagnosis, low Sokal risk score, number of previous treatments), the duration of deep molecular response before TKI cessation seems to be the most important factor to maintain treatment-free remission.

In conclusion, approximately half of patients who achieve a durable remission can be successfully discontinued from targeted therapy. Discontinuation can hopefully represent a cure for these patients.

Figure 1. Panel A. Meta-analysis of 20 studies evaluating the occurrence of molecular relapse after TKI discontinuation. Squares denote study-specific parameters, while diamonds indicate pooled parameters. $I^2$ is a measure of heterogeneity (accompanied by its level of statistical significance). CI confidence interval, EV number of events (numerator), TRT number of patients in the treatment group. Panel B. Temporal trend of duration of follow up and relapse rate evaluated by meta-regression of 20 trials. The graph shows the temporal trend of relapse estimated by meta-regression; p value: 0.515; meta-regression model: random effect; regression line: $y = 0.489 - 0.001 x$. Symbols: each study is represented by a circle the area of which is proportional to its statistical weight.
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