Therapy de-escalation before stopping in chronic myeloid leukaemia

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The treatment of chronic myeloid leukaemia (CML) has rapidly evolved since the invent of tyrosine kinase inhibitor (TKI) therapy. The efficacy of the first TKI, imatinib, was initially evaluated in the IRIS trial (started in June 2000) and shown to be superior to previous treatments.[1] Up to now, there is almost 20 years of experience of TKI therapy, and the current life expectancy of CML patients treated with TKI therapy equals age-matched healthy controls. Initially, genetic and molecular responses and the prevention of accelerated phase of CML with TKI therapy were important treatment goals. These goals are still valid, but currently when patient is diagnosed with chronic phase CML, many times the treating physician already discusses the possibility of treatment free remission in the future. During the last 10 years many treatment discontinuation trials have been performed, and they have evaluated the safety and efficacy of TKI discontinuation in CML patients who have achieved deep molecular remission (at least molecular remission 4, MR4). The long-term follow-up of the first larger STIM1 trial showed that with the median follow-up of more than 6 years, 43% of patients were still in remission after TKI discontinuation.[2] The EURO-SKI trial included over 700 patients and showed that at 24 months after TKI stopping the molecular relapse-free survival was 50%.[3] Based on these positive results, some of the current clinical guidelines already state that TKI discontinuation can be considered in selected patients outside the clinical trials.[4] Prerequisites for safe TKI discontinuation have been suggested: chronic phase of the disease, at least 3-5 years of prior TKI therapy, quantifiable BCR-ABL1 transcript, access to high quality monitoring, and stable molecular response (BCR-ABL1 ≤0.01% IS for more than 2 years).

In the *Lancet Haematology*, Clark and colleagues report the final results of the DESTINY trial evaluating the feasibility of TKI de-escalation before stopping, and its impact on the molecular relapse rates.[5] In addition, they include a previously mostly unstudied patient cohort, patients in major molecular remission MMR but not in stable MR4, to their clinical trial. Compared to other published TKI discontinuation studies these are both novel aspects since in previous studies TKI therapy have been stopped abruptly without de-escalation. It has even been considered that de-

escalation is not recommendable since it may allow the expansion of existing leukaemia cells and putative TKI resistant clones. The interim report of DESTINY trial published in 2017[6] showed that the de-escalation to half of the standard dose of therapy is safe and results to molecular relapse only in a minor fraction of patients (7% within 12 months of half-dose therapy). In the current final analysis of the study (12 months de-escalation followed by the TKI stop) they show that 36-month recurrent free survival is notably high, 72%, in the MR4 cohort (n=125). In the MMR cohort (n=49), this is clearly lower (36%), but it should be noted that still one third of the patients stay in remission after the TKI stop. Furthermore, sub-analysis suggests that one single PCR result at the trial entry is not optimal as it would have classified the majority of MMR patients to wrong MR4 cohort with different outcome.

As the rate of treatment free remission in the DESTINY trial is superior to previous studies, it raises the question what is the cause for this? Multivariate analysis of clinical factors only showed that the trial group (MR4 versus MMR) and the duration of TKI treatment predicted molecular recurrence. The predictive value of treatment duration has also been shown in previous studies, such as in the EURO-SKI study.[3] However, this cannot explain the difference in remission rates since the median duration of treatment in the DESTINY trial (6.9 years) does not differ from other trials. The authors speculate that TKI de-escalation may allow leukaemia stem cells to leave their quiescent state, and this may dispose them better to the effect of TKI treatment. Furthermore, the de-escalation phase may create an optimal window for immune system to respond and react to proliferating leukaemia cells. The importance of immune system has also been shown in conjunction with other stopping trials.[7-9] The more detailed biological understanding of the importance of both of these factors (leukaemia stem cells and immune system) in successful TKI discontinuation is highly warranted, and this study will hopefully create possibility for that in the future with advanced single cell sequencing techniques and available bone marrow samples collected during the trial.

But how to now translate these results to clinical practice? Should it be added to the guidelines that de-escalation is recommended instead of rapid TKI stop? As the treatment free remission rate with de-escalation is similar with the other trial using one-year maintenance therapy with interferon before total treatment discontinuation[10] it could also be asked are these same patients that benefit from both approaches or different patients? TKI stopping biology may be highly variable between individual patients, and “one size fits all” ideology would not be ideal here. All in all, this suggests that randomized TKI stopping trials with different treatment discontinuation

approaches should be performed in order to define the optimal stopping guidelines. These should be accompanied with translational studies and unified registries allowing meta-analysis before definite clinical guidelines advising optimal treatment discontinuation strategy can be set.

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