Long-term results of tyrosine kinase inhibitors discontinuation in patients with chronic myeloid leukemia

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Background

Evaluation of long-term follow-up results of treatment free remission (TFR) in chronic myeloid leukemia (CML) patients (pts) is relevant for the introduction of this approach into routine clinical practice.

Objective

To analyze the outcomes in a long-term follow-up of Russian cohort of CML pts who discontinued tyrosine kinase inhibitors (TKIs) therapy.

Materials & Methods

TKI treatment was discontinued in 185 CML pts with deep molecular response (DMR, at least MR4, BCR::ABL1≤0,01% IS, duration ≥1 year), including 113 pts in prospective RU-SKI trial and 72 pts in retrospective group out of the trial (toxicity, pregnancy, physician decision). Molecular relapse and TKIs restart was in case of major MR (MMR, BCR::ABL1>0,1%) loss. In pregnant pts TKIs were restarted in case of MR2 (BCR::ABL1>1%) loss.

Baseline characteristics of pts are shown in table 1: male 39%, median (Me) age was 43 (21-86) years. Me duration of TKI therapy was 7 (0,5-18) years. Second discontinuation was in 8 pts.

Kaplan–Meier analysis and cumulative incidence function were used.

Table 1. Characteristics of 185 CML patients at the time of TKI therapy discontinuation

Characteristics, n(%)	Parameters
Age, median (range), years	43 (21-86)
Gender: male / female, n (%)	72(39)/113(61)
TKI therapy duration, median (range), years	7 (0,5-18)
DMR duration, median (range), years	3,6 (0,1-11)
MR4.5 / MR4 / no data, %	62/11/27
TKI therapy before discontinuation:	
- imatinib, n (%)	124 (67)
- 2G-TKIs, n (%)	61 (33)
Pregnancy, n (%)	34 (19)
Second attempt of TKI STOP, n (%)	8 (4,3)

Results

Me time of follow-up without therapy was 6 years. Therapy was resumed in 96 (52%) pts with MMR loss and in 6 (3,2%) pts without MMR loss (DMR loss, withdrawal syndrome). Seven (3,8%) pts have died (not related with CML). In total, 80(43%) pts remained in TFR.

Survival without therapy at 3 and 5 years after TKI discontinuation was 45% (CI 37-52%) and 44% (CI 37-51%) respectively (figure 1A). In pts with first and second discontinuation survival without therapy was 45% versus 12,5% (p=0,004, figure 1B). The cumulative incidence of MMR loss at 5 years after TKI discontinuation was 51,5% (95% CI 45-59%) in all pts, 50% и 87% (p=0,03) in pts with first and recurring discontinuation accordingly (figure 1C.D). Loss of MMR between 1 and 3 year after TKI stop was in 9 pts, between 3 and 5 year – in 6 pts. There was no MMR loss after 57 months of follow-up. After 5 years of follow-up BCR::ABL1 level fluctuations 0,01% –0,1% were in 4 (5%) pts.

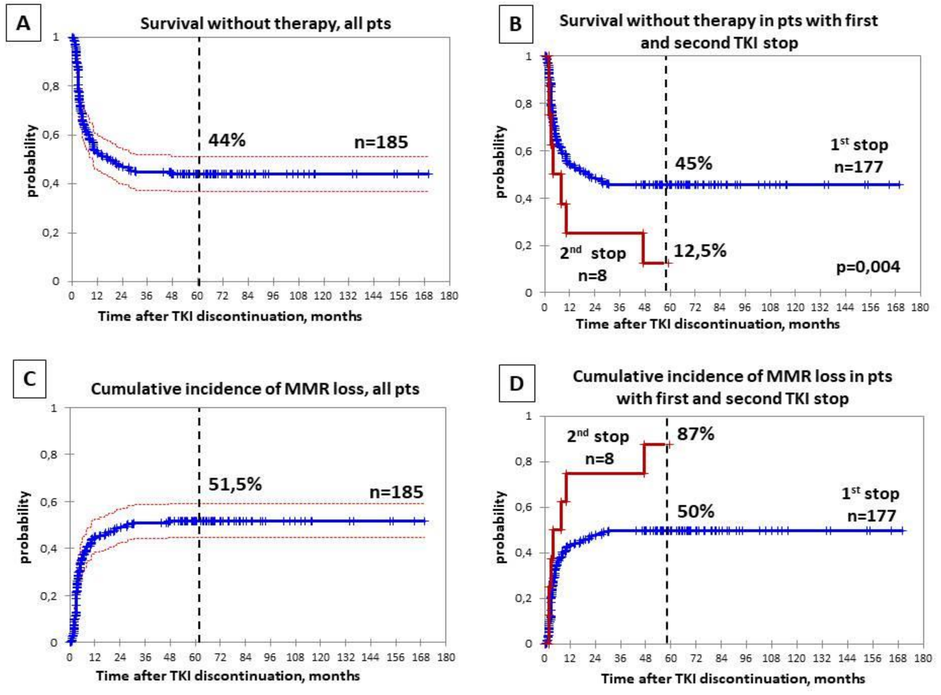


Figure 1. Survival without therapy and cumulative incidence of MMR loss in CML patients after TKI discontinuation

Summary

The probability of MMR loss after 5 years follow-up was 51,5%. Molecular relapses were rare after 2 years without TKI therapy. However, molecular monitoring with a frequency of 2-3 times a year during long-term observation in TFR is mandatory for pts safety, especially in those with detectable MRD.