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THE PROGNOSTIC FACTORS OF LATE MOLECULAR RELAPSES AFTER TREATMENT DISCONTINUATION IN PATIENTS WITH CHRONIC MYELOID LEUKEMIA

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INTRODUCTION

Molecular relapses in patients with chronic myeloid leukemia (CML) mostly occur within the first 6 months after tyrosine kinase inhibitors (TKIs) treatment discontinuation. The frequency of late molecular relapses (LMR) is 10-12% according to the literature (1), which determines lifelong molecular control in these patients. A TKI treatment duration before "stop" is an approved significant factor for the development of early molecular relapses. A search for simple and practical predictors of LMR is an important goal for a wider implementation of observation in treatment-free remission (TFR) in clinical practice.

AIM

To analyze the prognostic factors for LMR after TKIs discontinuation in CML patients in RU-SKI study.

METHOD

98 CML patients with TKI therapy duration ≥ 3 years and with deep molecular response (DMR, BCR::ABL1≤ 0.01% IS) duration ≥ 2 years were included in prospective study RU-SKI. The characteristics of the patients are presented in table 1.

Molecular relapse and TKI restart was defined as a major molecular response (MMR, BCR::ABL1>0,1%) loss, evaluated by real-time polymerase chain reaction.

We considered the loss of MMR more than 6 months after treatment discontinuation as LMR and used a 6-months landmark for LMR analysis. A Kaplan-Meier method for the cumulative incidence function (CIF) was used with the log-rank test for comparison and the Gray test for multiple comparisons.

Table 1. The characteristics of 56 patients, who were included in analysis

Characteristics	Values
Total patients, included in LMR analysis, n	56
Duration of TKI therapy at the time of discontinuation, Me (min-max), years	8,8 (3-16,2)
TKI before discontinuation: imatinib:2G-TKIs, n (%)	38(68):18(32)
Depth of MR during first 6 months after TKI discontinuation (max BCR::ABL1 %, IS):	
MR5 (undetectable), n (%)	23 (41)
MR4.5, n (%)	11 (20)
MR4, n (%)	10 (18)
MR3 (MMR), n (%)	12 (21)

RESULTS

Median time of follow-up without therapy was 55 months (8-78 months). Fifty six (57%) out of 98 patients remained in TFR during first 6 months after treatment discontinuation and were included in analysis. Subsequent loss of MMR was in 8 (14%) patients within a period of 8 to 47 months after TKI discontinuation, median time of MMR loss was 16 months. Survival without MMR loss was 92% (CI 86-99%), 89% (CI 81-97%) and 84% (CI 73-94%) at 12, 36 and 60 months after 6-months landmark respectively (figure 1).

We have found no differences in LMR probability depending on the previous duration of TKI therapy. Also no difference (p=0,317) in LMR probability was observed in patients' groups with undetectable BCR::ABL1 (n=23, MR5) and detectable BCR::ABL1 level (n=33) during the first 6 months after TKI discontinuation.

Next, we assessed the probability of LMR depending on the maximum BCR::ABL1 level during the 6 months after treatment discontinuation: MR3 (with loss of MR4), MR4, MR4.5 or MR5 (see table1). We united patients with MR4, MR4.5, MR5 into one group (MR≥4, n=44) and compared with the group of patients with MR4 loss (n=12). We confirmed the association between MR4 loss during the first 6 months and LMR development: the probability of LMR was 50% in the patients with MR3 versus 7% in patients with MR≥4 (p<0.0001, figure 2).

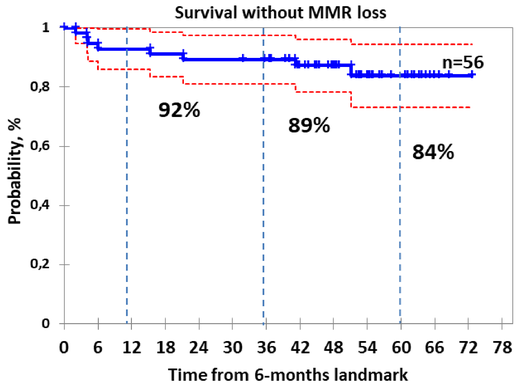


Figure 1. *Survival without MMR loss in 56 patients, who remained in TFR during 6 months after treatment discontinuation*

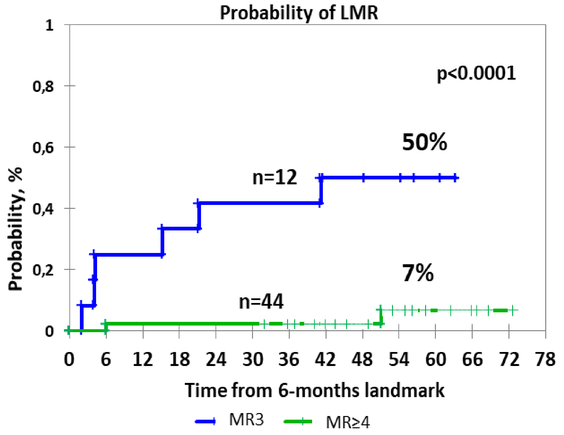


Figure 2. *Probability of LMR in patients with MR3 (MR4 loss) and MR≥4 during 6 months after treatment discontinuation*

CONCLUSIONS

- Only 14% patients, who maintained TFR during the first 6 months after treatment discontinuation, experienced late molecular relapses (LMR)
- Loss of MR4 in the first 6 months after TKI stop was the determining prognostic factor for the LMR probability
- The treatment duration did not affect the probability of LMR

REFERENCES

1. **Richter, J., et al.** Molecular status 36 months after TKI discontinuation in CML is highly predictive for subsequent loss of MMR—final report from AFTER-SKI. *Leukemia 2021; 35*, 2416–2418

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