# New Generation Tyrosine Kinase Inhibitors Versus Allogeneic Hematopoietic Stem Cell Transplantation in First Chronic Phase Chronic Myeloid Leukemia After Failure of at Least Two Tyrosine Kinase Inhibitors

O. KULEMINA MD[1], E. LOMAIA MD, PHD[1], YU.VLASOVA MD, PHD[2], YU.MATVIENKO MD[1], YU. YAKOVLEVA MD[2], E. OVSIANNIKOVA MD[1], N. SHNALIEVA MD[1], EU.SBITYAKOVA MD[1], E.MOROZOVA MD, PHD[2]

[1]Almazov National Medical Research Centre, St. Petersburg, Russian Federation. [2]Raisa Gorbacheva Memorial Research Institute for Pediatric Oncology, Hematology and Transplantation, Pavlov University, St. Petersburg, Russian Federation

## Introduction

Ponatinib and asciminib are highly effective new generation tyrosine kinase inhibitors (NG-TKIs) in heavily pretreated patients in chronic phase chronic myeloid leukemia (CP-CML). Meanwhile, allogeneic hematopoietic stem cell transplantation (HSCT) is recommended for patients who have failed two or more tyrosine kinase inhibitors (TKIs).

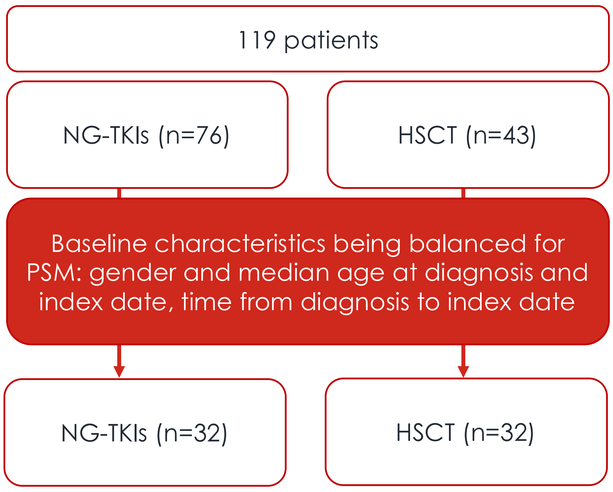
## Aim

This study aimed to evaluate long-term outcomes of patients treated with NG-TKIs versus HSCT.

## Methods

Data were collected from two Russian centers, including 119 adult patients with the first CP-CML who received either NG-TKIs (n=76) or HSCT (n=43) as first index therapy. Propensity score matching (PSM) was applied to balance clinically relevant baseline characteristics between the groups. After matching, 64 patients (32 per group) were included in the final analysis: NG-TKIs and HSCT. Up to 40% received ≥3 of TKIs before the intervention in both groups. Overall survival (OS) was estimated using the Kaplan-Meier method from the start of intervention to death or the last follow-up.

## Design




**Baseline charascterics for both groups:**

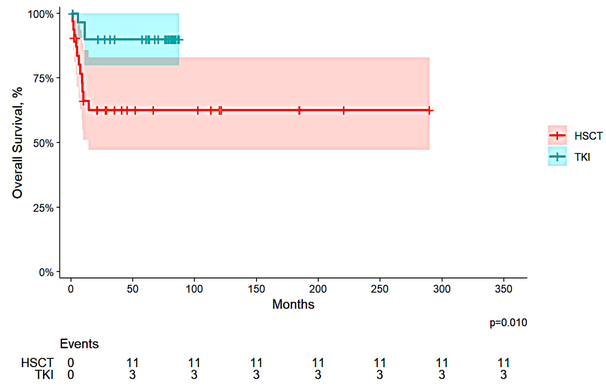
| | NG-TKIs (n=32) | HSCT (n=32) |
|---|---|---|
| Males, n (%) | 14 (44%) | 13 (41%) |
| Median age at diagnosis, years (range) | 37 (14-67) | 36 (17-58) |
| Median age at index date, years (range) | 40 (20-71) | 42 (19-61) |
| Time from diagnosis to index date, months (range) | 39.0 (5.4-284.6) | 44.3 (8.6-250.1) |

## Results

Median duration of NG-TKIs treatment and median follow-up were 49.3 (range, 0.5–85.8) months and 73.4 (range, 1.4–87.4) months, respectively. Median follow-up of HSCT group was 43.2 (range, 1.1–322.2) months.

At 24 months, OS was significantly higher in NG-TKIs compared to HSCT: 90.0% (95% CI: 79.9–100.0) vs 62.5% (95%CI: 47.2–82.9), respectively (*P*=0.010) (Fig1). All 3/32 (9.4%) deaths in NG-TKIs occurred in patients with a baseline *BCR::ABL1* transcript level >10%. In this subgroup, 24-month OS was 85.7% (95%CI: 72.0–100) with no statistical differences versus HSCT (*P*=0.058).

**Figure 1. Overall survival in HSCT versus NG-TKI groups**




*BCR::ABL* ≤1% was achieved in 12/24 (50%) and 8/8 (100%) patients with baseline *BCR::ABL* >10% versus *BCR::ABL* >1–10%, respectively (*P*=0.012). NG-TKIs treatment was discontinued in 18/32 (56%) patients, with all but one with baseline *BCR::ABL* >10%.

The most of patients (16/17, 94%) with molecular response 2 (MR2) also reached major molecular response (MMR). Treatment was discontinued in 18/32 (56%) of patients due to lack or loss response (n=9), toxicity (n=4) or other reasons (n=5). In HSCT group complete molecular response (=PCR negativity) was observed in 18/20 (90%) alive patients at the last visit. Other 2 patients failed stem cell engraftment – one of them was switched to second HSCT and is alive with PCR negativity status, the other patient is also alive with MMR reached on asciminib therapy. In HSCT group, 12/32 (37.5%) patients died, with all but one death attributed to HSCT-related complications. At the last visit, 18/20 (90%) alive patients had a complete molecular response.

## Summary

In our observation, OS was better with NG-TKIs versus HSCT in CP-CML patients who failed two or more TKIs. Meanwhile, patients with high baseline *BCR::ABL* levels were at higher risk of NG-TKI treatment failure. It seems that for this high-risk subgroup, particularly those with low transplant risk and a suitable donor, HSCT may be considered rather than NG-TKIs as ≥ third-line therapy.