XIX CONGRESSO NAZIONALE SIES2026
Firenze | 4-6 marzo 2026 Palazzo degli Affari

XIX Congress of the Italian Society of Experimental Hematology ABSTRACT N. P020

Myeloproliferative disorders

TREATMENT-FREE REMISSION ATTEMPTS IN CHRONIC MYELOID LEUKEMIA PATIENTS TREATED WITH SECOND- AND THIRD-GENERATION TKIS: A REAL-LIFE EXPERIENCE

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Introduction: Treatment-free remission (TFR) has become an achievable goal for many patients with chronic myeloid leukemia in chronic phase (CML-CP) treated with tyrosine kinase inhibitors (TKIs). While TFR feasibility has been widely demonstrated in clinical trials, the durability of TFR and the management of withdrawal symptoms remain clinical challenges. Moreover, dose reduction may favorably modulate disease kinetics and patient adaptation, potentially increasing the likelihood of successful TFR. We analyzed outcomes and tolerability in a real-life cohort of CML-CP patients treated with second- and third-generation TKIs who attempted first (TFR1) and second (TFR2) treatment discontinuation by TKI de-escalation.

Methods: :Forty-six CML-CP patients treated with nilotinib (n=38), dasatinib (n=4), bosutinib (n=2) or ponatinib (n=2) were retrospectively evaluated. All had maintained a deep molecular response (DMR; MR^4.5) for at least 2 years and 42 patients (90%) underwent a de-escalation phase for 6–12 months, with TKI doses reduced by 50% before discontinuation. Molecular monitoring was performed monthly for the first 6 months, then every 2–3 months. Loss of major molecular response (MMR) prompted immediate TKI reintroduction. Patients who regained DMR after TKI resumption were considered eligible for a second discontinuation attempt (TFR2). Adverse events (AEs) were systematically recorded during TKI withdrawal.

Results: At the time of TFR1, median patient age was 58 years (range 34–77), with a balanced sex distribution. Twenty-seven patients (58%) successfully maintained DMR during TFR1 for a median of 30 months (range 6–72), whereas 21 (42%) experienced molecular relapse and restarted therapy. Among relapsing patients, 18 (85%) regained DMR within 6 months of TKI reintroduction; 10 of these subsequently attempted TFR2, and only 4 (40%) achieved sustained TFR at a median follow-up of 14 months. Overall, 31 of 46 patients (67%) remained in durable TFR (either after TFR1 or TFR2). The TFR success rate was significantly higher in patients previously undergoing TKI dose de-escalation (67% vs 38%, p=0.04). Withdrawal-related AEs occurred in 70% of patients. The most frequent were arthralgias in 32/46 (69%), headache in 24/46 (52%), insomnia in 8/46 (17%), depression in 2/46 (4%), and thromboembolic events (TVP) in 2/46 (4%). Symptoms were generally mild and self-limiting, though transient TKI reintroduction or symptomatic therapy was required in 6 cases (13%). No disease progression or loss of hematologic response was observed.

Conclusions: In this real-world cohort, more than half of CML-CP patients treated with second- and third-generation TKIs achieved durable TFR after discontinuation, confirming the feasibility of TFR outside clinical trials. A second discontinuation attempt (TFR2) was successful in most patients who previously relapsed but regained DMR, suggesting that rechallenge is clinically reasonable in selected cases. Importantly, a structured dose de-escalation phase before TKI discontinuation was associated with improved TFR maintenance, suggesting that gradual tapering may facilitate immune re-equilibration and mitigate withdrawal-related cytokine rebound. These findings support dose de-escalation as a safe, effective, and pragmatic strategy to optimize treatment discontinuation decisions and improve the long-term success of TFR in CML-CP patients.