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Outcomes following treatment discontinuation in chronic myeloid leukaemia (CML): real-world experience from 3 regional UK centers

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INTRODUCTION

Survival for CML prior to the discovery of tyrosine kinase inhibitors was only approximately up to 7 years. Since the introduction of TKIs, many patients have a near-normal life expectancy.[1]

Evidence from clinical trials have demonstrated that TKIs can be safely stopped in some chronic-phase CML patients who have achieved deep molecular response, with the aim of treatment-free remission. The first study to demonstrate feasibility of stopping Imatinib was the STIM trial in France in 2010.[2] Following this, the EUROSKI study published in 2018 was able to replicate these results.[3] Importantly, these studies showed that majority of patients who experienced relapse following discontinuation were able to re-achieve molecular responses after re-initiation of TKI therapy.

Subsequent clinical trials including the STOP 2G-TKI, DASFREE, DESTINY, ENEST freedom trials have demonstrated feasibility of stopping 2nd generation TKIs, nilotinib and dasatinib for patients achieving deep molecular response.[4-7] Nilotinib is the only TKI with discontinuation eligibility and management in its Summary of Product Characteristics.[8]

Despite clinical studies showing favourable outcomes, real world data regarding feasibility and stopping TKIs for reasons other than achieving deep molecular response (particularly drug toxicity) is limited.

The British Society of Haematology released guidelines for the management of CML in July 2020, which included recommendations for discontinuation of TKIs.[9] The guideline recommends patients have at least 2 years of MR4 and at least 3 years (preferably 5) of TKI treatment. Follow-up recommendations include monthly blood tests for first 6 months, 6 weekly from 7 to 12 months, 2-monthly from 13-36 months, and 3 monthly from year 3 onwards. TKI therapy should be re-started within 1 month of loss of MMR.[9] This is similar to guidelines released by the American National Comprehensive Cancer Network (NCCN) and European Leukaemia Network (ELN) guidelines with slightly different follow-up monitoring requirements.[10-11]

AIM

The aim of this study was to address real world outcomes of treatment discontinuation and the factors influencing this.

METHOD

A retrospective analysis of all chronic phase-CML patients who had discontinued TKI treatment since 2010, from 3 hospitals in Birmingham was conducted. Patient who had prior non-TKI therapies were also included.

Relapse was defined as loss of Major Molecular Response (MMR) or Complete Molecular Response (CMR). Patients who relapsed were restarted on TKI.

Factors evaluated in this retrospective analysis include:
- Tyrosine Kinase Inhibitor used
- Line of treatment (Frontline or other)
- Reason for TKI discontinuation
- Remission status at the time of discontinuation
- Duration of remission status at the time of discontinuation
- Duration of TKI therapy prior to discontinuation
- Relapse rate
- Time between discontinuation to relapse
- Treatment-free survival

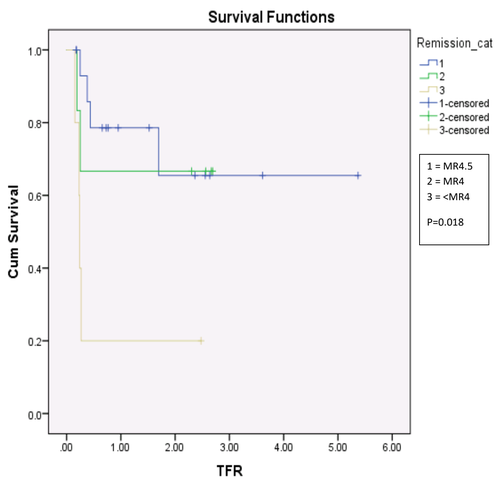
RESULTS

Patient Demographics
28 patients (11 males and 17 females) had stopped TKI therapy. The median duration of TKI treatment prior to discontinuation: 8.9 years (range 4.3-15.2). The median age at discontinuation was 61 (range 18-33).

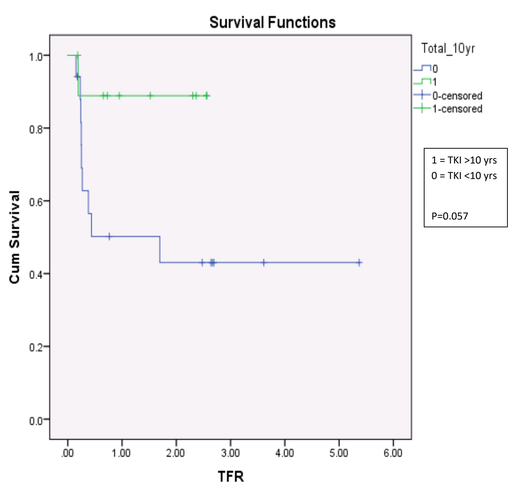
Factors Prior to Discontinuation	Outcomes following Discontinuation
Line of Therapy Frontline – 78.6% (n = 22) Second or third line – 21.4% (n = 6)	**Median treatment free remission (TFR)** Not reached (median follow up of 2.5 years)
Type of TKI Imatinib – 78.6% (n=22) Nilotinib – 10.7% (n=3) Dasatinib - 10.7% (n=3)	**Relapse Rate** 35.7% (n=10) • 90% (n=9) in first 6 months • 10% (n=1) >6 months • 60% (n=6) re-achieved MMR on re-starting TKI
Reason for Discontinuation of TKI • Patient preference – 10 • Enrolment in stop TKI trial – 9 • TKI Drug toxicity - 8	**Relapse Rate in first 6 months after TKI discontinuation by Remission Status** MR4.5: 18.5% (3 of 16 patients) MR4 : 33.3% (2 of 6 patients) MR <4: 80% (4 of 5 patients)
Remission status at time of TKI discontinuation 17 patients (60.7%) achieved MR4.5 6 patients (57.1%) achieved MR4 5 patients (17.9%) achieved MR<4	**Other Medical Outcomes** Withdrawal syndrome – 1 Death (second malignancy unrelated to CML) - 2
Duration of deep molecular remission prior to TKI discontinuation 16 patients (57.1%) had DMR (MR4 or MR4.5) for at least 5 years • 11 of these patients had MR4.5 for at least 5 years.	

Factors Influencing Treatment-Free Remission

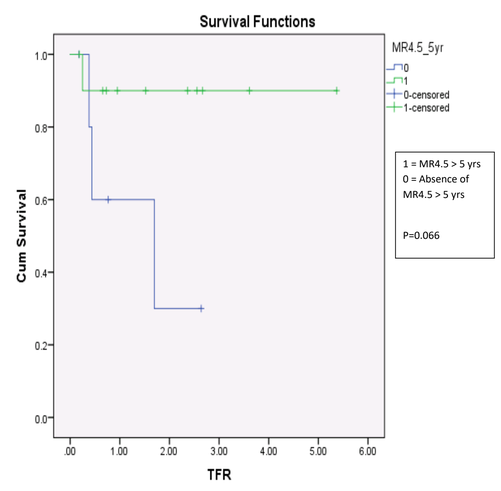
1. Remission Status



2. Duration of TKI treatment



3. Duration of MR4.5



Factors which did NOT Influence Treatment-Free Remission
1. Reason for discontinuation of TKI
2. Line of TKI therapy
3. Type of TKI

CONCLUSIONS

Real world outcomes from our study are largely consistent with published data on TKI discontinuation in CML, demonstrating feasibility of discontinuation in clinical practice. As shown in previous clinical trials, this study demonstrated that treatment free remission is significantly correlated with depth of molecular response, and duration of TKI treatment prior to discontinuation. Results from this study show unfavourable TFR in MR<4, which is in keeping with the BSH guideline recommendations. By providing real-world data, our study may give additional confidence to clinicians on TKI discontinuation.

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