CML HORIZONS

HYBRID MEETING 2024

Vilnius, Lithuania
24–26 May 2024

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TFR Monitoring and Protocols in LMICs (Low- to Middle-Income Countries)

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INTRODUCTION

- Management of Chronic Myeloid Leukaemia (CML) with tyrosine kinase inhibitors has dramatically changed the treatment landscape of the disease

- Many patients now have good quality of life and have the opportunity to live their lives to the best of their abilities

- A new era has however emerged in the management of CML where the possibility of stopping TKI and remaining disease –free has become a reality

- Treatment-free remission (TFR) is defined as stopping tyrosine kinase inhibitor (TKI) therapy after achieving a sustained deep molecular response (DMR) and remaining in a deep molecular response without treatment[1]

- Initially tried in a clinical trial setting TFR is now a treatment in the clinic

- Not everyone however will be eligible or have a successful TFR outcome

Hughes TP and Ross DM. *Blood*. 2016 Jul 7;128(1):17-23

Lessons learnt from Clinical Trials on TFR

- A pilot study (STIM)proved that imatinib discontinuation was possible in selected CML patients
- After a median follow-up of 18 months, 50% of patients remained off therapy without confirmed reappearance of BCR-ABL transcripts in peripheral blood
- After 7.5 years follow up (range: 4.4 – 8.4 years) 50% of patients werestill off therapy with an undetectable level of BCR-ABL transcripts
- Since then several clinical trials have been conducted on TFR from different parts of the world

- These trials have made it possible to take TFR to the clinic and make it a treatment option for CML in the real world.
- Based on the findings of these trials its been established that the longer a patient is exposed to TKIs the better the outcome of TFR
- Also achieving MR4.5 sustained for 2 years increases the success rate
- History of resistance, relapse and complex mutations do not lend to favourable outcomes
- These have informed the various criteria used to implement TFR in the clinic
- Successful outcomes of TFR currently implemented in small single centres different parts of the world ranges between 56-72%

Hoosen et al
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Moving treatment-free remission into mainstream clinical practice in CML

Timothy P. Hughes and David M. Ross

Blood 2016 128:17-23; doi: https://doi.org/10.1182/blood-2016-01-694265

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Summary of key inclusion criteria and TKI retreatment triggers used in clinical trials

Study	TKI	Number of patients reported	Required depth of MR	Minimum duration of MR (years)	Trigger to resume TKI
STIM[20]	Imatinib (±prior IFN)	100	UMRD (MR5.0)	2	Loss of UMRD*
TWISTER[21]	Imatinib (±prior IFN)	40	UMRD (MR4.5)	2	Loss of UMRD
A-STIM[22]	Imatinib (±prior IFN)	80	UMRD†	2	Loss of MMR
EuroSKI[24]	Imatinib/nilotinib/dasatinib	200	MR4.0	1	Loss of MMR
Stop 2GTKI[28]	Nilotinib/dasatinib first and second line	52	UMRD (MR4.5)	2	Loss of MMR
KIDS[25]	Imatinib (±prior IFN)	90	UMRD (MR4.5)	2	Loss of MMR
HOVON[32]	Imatinib	18	UMRD (MR4.5)	2	Loss of UMRD
DADI[27]	Second-line dasatinib	63	MR4.0	1	Loss of MR4.0
STIM2[26]	Imatinib	124	UMRD (MR4.5)	2	Loss of UMRD

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Institutional requirements for safe supervision of TFR

1. Availability of high quality internationally standardized, accurate, sensitive RQ-PCR laboratory
2. Rapid turn-around of RQ-PCR test results, within 4 weeks
3. Capacity to provide RQ-PCR tests every 4-6 weeks, when required
4. Structured follow-up established to enable rapid intervention if BCR-ABL is rising

Clinical and Monitoring Requirements

LALNET vs ELN recommendations

	LALNET 2021	ELN 2020
Duration of TKI therapy	>5 years for all TKI	>5 years **> 4 years for 2nd generation TKI**
Molecular response	MR4.5 for >2 years	**MR4.0 > 3 years** **MR4.5 > 2 years**
Disease phase	Chronic phase	Chronic phase
BCR-ABL transcript type	E13a2 , e14a2	E13a2 , e14a2
Previous TKI resistance	TFR not recommended	TFR not recommended
Trigger for TKI reintroduction	Loss of MMR	Loss of MMR
Monitoring after discontinuation	Monthly 1-6 m Every 2-3 months: 6-12 m Every 3 months >12m	Monthly 1-6 m **Every 2 months: 6-12 m** Every 3 months >12m
Access to high quality PCR	Yes	Yes

CURRENT STATUS OF MANAGEMENT OF CML in LMIC

- TKI access have indeed revolutionized the management of CML
- Patients not only achieve haematological remission but go on to attain cytogenetic and molecular remissions
- Hitherto hydroxycarbamide was the main treatment option for most and achieving a sustained haematological remission was a problem
- Number of people diagnosed with CML have also increased

- Currenty the urge among patients in LMIC to be part of TRF increases daily

- The question is, “are the challenges faced in implementing TFR in LMIC surmountable?”

- Selection of patients, institutional requirements and safe monitoring which forms the backbone of TRF is possible when certain structures and facilities are in place.

ELN 2020 Recommended Requirements Prior to Considering Stopping TKI Therapy in CML

Mandatory	Optimal	Minimal
CML in 1st Chronic Phase	Duration of TKI therapy >5yrs	1st line TKI or 2nd line if intolerance was the only reason for switching
Motivated patient	Duration of DMR >3yrs if MR^4	Typical e13a2 or e14a2 BCR-ABL1 transcripts
Access to rapid turn-around BCR-ABL1 PCR	Duration of DMR >2yrs if $MR^{4.5}$	Duration of TKI therapy >5yrs if imatinib, or >4yrs for others
Patient agreement to more frequent monitoring	-	Duration of DMR (MR^4 or better) >2yrs
-	-	No prior treatment failure

What Are The Most Significant Barriers To TFR In LMIC

- ACCESS TO TESTING
- AFFORDABILTY
- EARLY DETECTION
- READY ACCESS TO TKIs
- PSYCHOLOGICAL ASPECTS OF TFR (Patient and Physicians)

- Diagnostic and monitoring equipment are few and inadequate for the number of patients who need it in LMIC

- Frequent PCR tests required will be costly and for most patients in LMIC, payment is out of pocket.

- Late presentation by patients to health facilities in LMIC lead to advanced disease which is characterized by complex mutations that have an impact on prognosis

- Achieving complete molecular response or major molecular response then becomes more difficult

- Quite a number of centers do not have ready access to all the different generations of TKIs

Making TFR A Reality In LMICs

- FREQUENT TESTING (access to testing and affordabilty)
- COMPLIANCE TO THERAPY
- EARLY DETECTION
- READY ACCESS TO ALL THE DIFFERENT GENERATIONS OF TKIs
- ADDRESSING PSYCHOLOGICAL ASPECTS OF TFR (PATIENT AND PHYSICIAN)

- More PCR machines are needed, testing has to become affordable and institutions need to improve upon structures and services.

- Awareness creation through education which will lead to early detection of CML and also a deeper understanding of TFR as a current treatment option

- Ready access to TKI will also be a source of security reassuring for both providing a “safety net” in cases of relapse for both patients and physicians

- All stakeholders: Advocates , Patients, Clinicians, Governments, Private sector and Non – Governmental Organizations need to come together to make TFR a treatment option especially in LMIC

- Addressing the psychological aspects TFR for both patients and physicians

CONCLUSION

- TFR despite challenges is a new treatment option for people living with CML in LMIC
- Early detection, improving access to affordable testing , educating and sensitizing people living with CML and physicians as we as maximizing available resources are key
- With a united effort TFR is possible in LMIC

THANK YOU

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