Leukaemia Care
YOUR Blood Cancer Charity

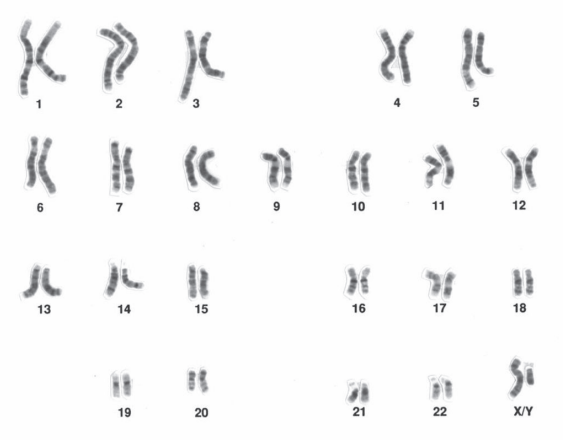
Advocacy toolkit

CML and Treatment Free Remission

In this toolkit, we take a look into the treatments for Philadelphia-positive Chronic Myeloid Leukaemia (CML) that have led to treatment free remission (TFR) being one of the biggest topics on the agenda for CML.

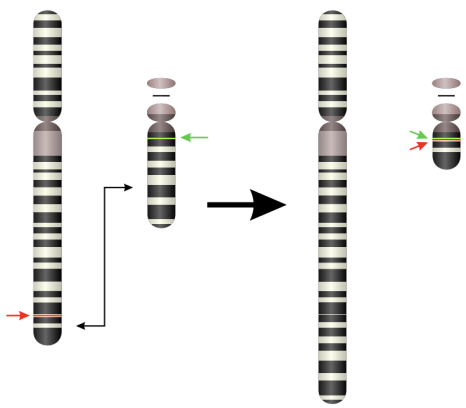
Philadelphia Positive (Ph+) Chronic Myeloid Leukaemia

Every human cell should contain within the nucleus 22 pairs of chromosomes, plus 2 sex determining chromosomes that are either XX (Female) or XY (male). The chromosomes contain all the genes required for human life.



1) Set of human chromosome (male).

In the 1960's researchers identified that the cells from CML patients contained an unusually short chromosome and this was named after the location of its discovery, the Philadelphia chromosome.



2) The formation of the Philadelphia chromosome by translocation between chromosomes 9 and 22

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It wasn't until later that researchers were able to identify that the Philadelphia chromosome had been formed by regions on chromosome 9 and chromosome 22 swapping (translocation). The swap occurs at a very specific point, causing the ABL gene on chromosome 9 to be joined to the BCR gene on chromosome 22 and hence a new gene is formed, BCR-ABL

From BCR-ABL a type of tyrosine kinase is produced. This is an enzyme involved in cell signalling, which turns genes on and off. The effect of the BCR-ABL tyrosine kinase signalling is uncontrolled cell division of white blood cells; hence it is a driver of CML.

The Philadelphia chromosome is present in approximately 95% of CML cases.

Tyrosine Kinase Inhibitors (TKI)

In the 1990's, an American oncologist, Dr Brian Druker was researching into the use of tyrosine kinase inhibitors (TKIs) for the treatment of CML. These inhibitors prevent the cell signalling activity of tyrosine kinases.

Dr Druker began working with the pharmaceutical company Ciba-Geigy (now Novartis) who had been developing a range of TKIs and eventually came across a compound that reduced CML cells by over 90% in samples of human bone marrow within the lab. This compound was named imatinib, and human trials for the treatment began in 1998.

In 2001, imatinib (brand name Gleevec) was approved for use within the USA for treatment of CML. It was the first treatment to be developed that targeted a specific cancer-causing gene alteration. Since this time, a number of other TKIs have been developed for the treatment of CML four of which are routinely used in the UK: nilotinib, dasatinib, bosutinib, ponatinib.

Effectiveness of TKI drugs

Prior to the introduction of TKI drugs in 2001, only 30% of patients survived 5 years following diagnosis. In one of the first trials of imatinib, 53 out 54 patients achieved complete haematological response, meaning their white blood cell counts returned to normal. In the following 5-year follow up trial, 89% achieved 5-year survival.

Today the five year survival is likely to be higher than 89%. This is because, with the advent of further TKI drugs, there are now more potent options for those who fail to respond to, or become resistant to, imatinib.

Most patients today will live a normal lifespan by taking TKI drugs on a daily basis and, more often than not, face greater side-effects from TKI side-effects than CML itself.

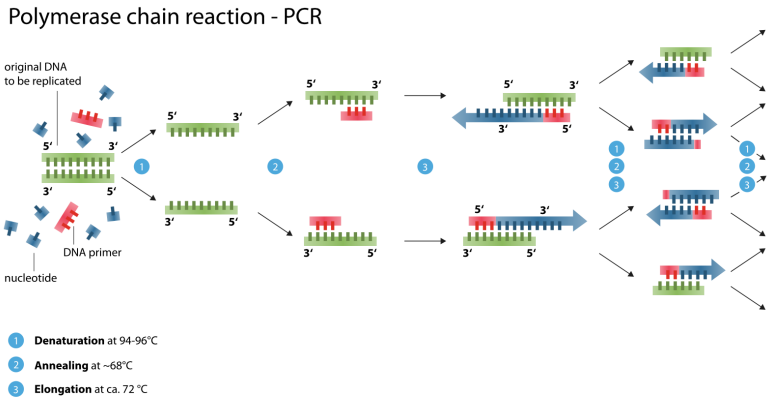
Treatment Free Remission (TFR)

The majority of CML patients using TKI drugs will have very little detectable disease using the most sensitive method of detection, PCR (polymerase chain reaction).

PCR (Polymerase Chain Reaction)

PCR is the process of copying a DNA segment (in this case, the BCR-ABL gene segment) multiple times over to increase the amount (amplification) and enable detection.

This method allows detection of 1 CML cell in up to 100,000 cells (0.001%).



At this level, the amount of disease is defined by:

- Major Molecular Response (MMR) or MR^3 – this refers to a log reduction of 3, or 1000 times fewer BCR-ABL than would be expected to be found in an untreated CML patient.

- Deep Molecular Response (DMR) or $MR^{(4.5)}$ – this is smallest amount of BCR-ABL that can be detected by PCR, with between 10,000 to 100,000 times fewer BCR-ABL than would be found in untreated CML.

In recent years, the question has arisen whether patients who have achieved DMR with TKI drugs could stop their treatment and sustain DMR – this is known as treatment free remission (TFR).

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Who can consider TFR?

There are many clinical trials ongoing for TFR that patients can join. The main condition for trials is that patients need to have achieved and sustained DMR for a number of years prior to attempting TFR.

One unusual exception to this is the DESTINY trial, that recruited a cohort of patients who had achieved MMR but not DMR. In this trial, the TKI drugs were reduced to half dose for 12 months before full removal of the drugs – in most trials this de-escalation does not occur.

In recent years, however, more clinicians are attempting TFR with their patients outside of clinical trials. Mainly due to the lack of availability within trials, and secondly because there is better guidance on safely attempting TFR outside of trials. Nilotinib, however, is currently the only TKI to contain TFR within the marketing authorisation – this defines how a drug is presented for use within Europe by the manufacturer. It states:

'Treatment should continue for as long as the patient continues to benefit. The dose should be reduced or treatment interrupted if the patient has certain side effects affecting the blood. Stopping treatment may be considered in patients in chronic phase after treatment with Tasigna for at least 3 years, whose disease has been well controlled for at least 1 year.'

The European Society of Medical Oncology (ESMO) have published guidelines for considering patients to attempt TFR within the clinical setting:

1) Need to ensure 'proper, high-quality and certified monitoring'.

Patients attempting TFR need to be closely monitored, with PCR tests guaranteed every month for at least 6 months, every 6 weeks for 6 months and every 3 months thereafter. The results also need to be reported on in a timely manner, to ensure that patients who's BCR-ABL levels start to increase are recognised as early as possible.

Generally, this criterion is less of an issue within the UK compared to some other countries where, for example, PCR is not routinely available.

2) Typical BCR–ABL1 transcripts identified at diagnosis.

PCR for recognition of the typical BCR-ABL gene segment is very strictly regulated and standardized across the globe. However, around 2-3% of patients have slightly different BCR-ABL gene mutations (atypical), which makes identification of CML cell levels less accurate and hence, the advice is to avoid attempting TFR.

3) Must have received TKI therapy for a minimum of 5 years

4) Achievement of MR^(4.5) and sustained DMR for at least 2 years

5) Informed consent of the patients

Patients must be given full information surrounding risk of relapse, requirements for regular testing and potential side-effects (see below).

NB Do not attempt TFR and stop taking your TKI drugs without this being discussed, agreed and overseen by your clinician first.

Are there any risks associated with attempting TFR?

Side effects: TKI withdrawal syndrome

Patients involved in clinical trials have reported musculoskeletal problems following TKI withdrawal, normally localised within the hips, shoulders and/or extremities. In some cases, it appears TKI treatments improve the symptoms of arthritis which are similar to those reported during TKI withdrawal symptom. Hence, stopping treatment can reveal arthritis.

In most cases, TKI withdrawal syndrome is mild enough to be managed by over-the-counter medicines and cease over time . It was suggested in the DESTINY trial that gradual removal of TKIs could possibly help to reduce the effects of TKI withdrawal syndrome.

Emotional impact

Moving away from taking a drug every day and having a stable response can be a big step. Some patients express feelings of anxiety and fears about relapsing with attempting TFR.

What are the advantages?

A sense of 'normality'

Patients who achieve TFR express the feeling of 'normality' that comes with not taking a drug every day and living free from both the side-effects of TKIs and CML symptoms.

Reduced side-effects from TKI therapies

As mentioned previously, many patients respond very well to TKIs but are left with side-effects due to the toxicities of treatment and risk of adverse events increases with long-term use of TKIs. This can significantly impact the quality-of-life of patients.

Successful TFR, therefore, may mean overcoming the quality-of-life limiting side-effects. Although, the musculoskeletal issues associated with TKI withdrawal syndrome experienced in around 15-30% of patients must be considered.

Cost benefits

The cost of using TKI treatments over the lifetime of a CML patient can be significant. For example, the annual cost for one patient using dasatinib treatment is £30,477.00 per year . This cost is variable dependent on the dosage required by the patient and the introduction of generic drugs has significantly reduced costs.

You can read about generic drugs in our advocacy toolkit.

Fortunately, within the UK patients are not directly responsible for covering the cost of their healthcare. However, there will be a significant cost saving for the NHS not having to pay for treatment for those who can achieve sustained TFR. These funds could then be redirected for other healthcare benefits.

How many patients achieve TFR?

There is a chance that patients see an increase in their CML levels upon removal of TKIs and lose Major Molecular Response (MMR). Studies have clearly shown, however, that patients can safely restart TKI treatment and achieve DMR again without any apparent impact on long-term outcomes.

Evidence from trials demonstrates that around 40% to 50% of patients achieve long-term TFR. The majority of patients who lose MMR will do so within the first 6 months and after this time, the risk is around 10% up to 24 months TFR.

There are several factors that appear to correlate with patients attaining TFR:

1) Early molecular response (EMR) to TKIs

Early molecular response to TKIs is one of the key prognostic indicators for patients and it is correlated to patients later achieving MMR or DMR . Therefore, it could be the case that patients with EMR are more likely to achieve TFR later down the line.

2) Longer TKI treatment and sustained DMR

A clear factor that appears to influence TFR is how long the patient has sustained DMR with TKI treatment prior to attempting TFR.

For example, the EURO-SKI early data analysis found a loss of MMR within 6 months in 47% of patients treated with TKI for less than 8 years, compared to 26% of those who had been treated for more than 8 years.

3) The type of TKI patients are treated with

All TKIs inhibit the activity of the BCR-ABL gene, as suggested by the name, however, there are differences between the TKIs in both how they function and how well targeted they are.

Imatinib is less toxic than other TKIs, but those developed after are generally more effective for achieving DMR. Due to this, studies have shown that more patients treated with nilotinib, for example, will be able to attempt TFR than those on imatinib. Hence, the numbers of patients achieving TFR will be greater for those previously treated with nilotinib.

Is TFR a cure?

Some patients feel as though stopping their treatment and living in TFR as a cure, however, the clinical community is cautious to say this.

This is because, the slowly progressing nature of CML and the older age patients may mean that MMR is not lost in patients within their life-span. However, there is still risk that given enough time the leukaemia cells will begin to increase above MMR and the EURO-SKI trial has demonstrated late-relapses after years of TFR. In this vain, patients will require regular, life-long PCR monitoring to assess disease burden.

Cure, or not, the opportunity for patients to attempt TFR and live treatment-free for an extended period of time may go far in contributing to increased quality-of-life.

TFR and the patient perspective

To learn more about TFR and the things to consider it is good to hear from the patients themselves.

In the following link you can watch and hear from a CML advocate their perspective:

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"The bottom line I think is, TFR is not well understood and there is much confusion [for patients] but, as much, we also have the hope and excitement of being able to stop treatment."

https://vimeo.com/220445487

Our own trustee and CML patient Kris Griffin also speaks about his views on TFR here:

"Sometimes, in around about 40% of cases, the leukaemia doesn't come back, which I think is incredible. It's incredible for people who struggle with side effects in particular. I can use this because I'm a patient, but I think that's a cure."

https://www.youtube.com/watch?v=Etw3GuZvW-s

Further questions

If you have any further questions about treatment free remission (TFR) then you can contact our Campaigns and Advocacy team. They are available Monday to Friday from 9:00am – 5:30pm. If you would like to speak to them, you can:

- Call our office line on 01905 755977
- Send them an email at advocacy@leukaemiacare.org.uk
- You can also call the help line, free of charge on 08088 010 444. The team will pass your enquiry onto the Campaigns and Advocacy team.

Please note that our Campaigns and Advocacy team are unable to provide:
- Detailed medical advice or recommendations
- Legal advice
- Advocacy for a course of action which is contrary to the aims and objectives of Leukaemia Care.

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