

# TREATMENT FREE REMISSION ASSESSMENT AFTER DISCONTINUATION OR DOSE REDUCTION OF TYROSINE KINASE INHIBITORS IN CHRONIC MYELOID LEUKEMIA PATIENTS

## **Abstract:**

Chronic myeloid leukemia (CML) is more than ever the model of targeted therapy for human malignancies. The success of imatinib and second-generation tyrosine kinase inhibitors (TKIs) has dramatically changed the outcome for CML patients. Since TKI-treated CML patients have a near-normal life expectancy, two important issues must be considered in the future: (1) the quality of life and ethical aspects of the treatment and (2) the economic impact of treating patients during lifetime. One of the best ways to consider these two points is to ask the question about stopping TKI in good responder patients. Such strategy has been proposed now in several studies, and thousands of patients have officially stopped TKI around the world for molecular efficacy in clinical trials.<sup>(1,2)</sup>

**Keywords:** Chronic Myeloid Leukemia, TKI Discontinuation, Treatment Free Remission

## **1.Introduction:**

Chronic myelogenous leukaemia (CML) is a clonal disease that is typically easy to detect since the malignant cells of more than 95 percent of patients exhibit a specific chromosomal aberration known as the Gene mutation (Ph). The Ph is caused by a reciprocal translocation of the long arms of chromosomes 9 and 22 (t 9; 22) and may be seen in all hematopoietic progenitors. This translocation leads in the translocation of the Abelson (ABL) oncogene from chromosome 9 to the breakpoint cluster region of chromosome 22. (BCR). This results in a fusion of the BCR/ABL genes and the synthesis of an aberrant tyrosine kinase protein, which produces the disorganised myelopoiesis seen in CML<sup>(3)</sup>

TKIs that target the ABL1 tyrosine kinase have significantly improved the prognosis of CML patients. Indeed, when TKI therapy is used correctly, it can lead to an excellent molecular response and a life expectancy that is comparable to that of the general population in the majority of CML patients.<sup>(1, 2)</sup>

Although the ELN (European Leukemia Network) guidelines for the management of CML recommend that TKI therapy be continued indefinitely in all responding patients, the most recent NCCN (National Comprehensive Cancer Network) guidelines, based on the most

recent studies on treatment-free remission, support the view that treatment can be interrupted in a select group of patients<sup>(3, 4)</sup> However, because all TKIs are unable to eradicate quiescent leukemic stem cells, the majority of patients will require TKI therapy to be continued permanently, as the majority of patients will relapse if treatment is stopped.<sup>(5, 6)</sup>

Nonetheless, lifetime TKI therapy may have side effects, such as chronic, mostly minor adverse events that can have a significant influence on patients' quality of life, adherence to therapy, and, as a result, treatment success. Several clinical discontinuation trials conducted in the last few years have shown that 40–60% of chronic phase CML patients (CP-CML) who have achieved a stable deep molecular response (DMR), defined as a sustained molecular response of at least 4.5(MR<sup>4.5</sup>), can cease treatment without relapse.<sup>(7, 8)</sup>

Other factors linked to a successful treatment-free remission (TFR) include a low Sokal risk group at diagnosis, chronic phase patients, optimum TKI response, prolonged TKI therapy (> 8 years), and longer DMR (> 2 years).<sup>(7)</sup>

The majority of patients who relapsed within 6 months after stopping TKIs remained sensitive to retreatment and regained at least a major molecular response (MMR), according to all published trials .<sup>(7, 8)</sup>

Furthermore, dose reduction in patients who respond well to TKI therapy can reduce the side effects while maintaining a deep molecular response.<sup>(14)</sup>

**2. Patients & Methods:** The work was conducted on 40 adult CP-CML patients with deep molecular response for two years or more from Maadi Armed Forces Hemato Oncology Hospital in Cairo and Alexandria Main University Hospital, divided into two equal groups either discontinuation of TKIs or dose reduction studied for continuous deep molecular remission over 12 months follow up period with reverse transcription and real-time quantitative polymerase chain reaction (RQ-PCR) for BCR-ABL every 6 weeks .

## 2.1 Statistical analysis of the data:

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Qualitative data were described using number and percent. Quantitative data were described using range (minimum and maximum), mean, standard deviation, median and interquartile range (IQR). Significance of the obtained results was judged at the 5% level.

### The used tests were :Kaplan-Meier

Kaplan-Meier Survival curve was used for the relation with Treatment Free Remission and dose reduction.

## 3. Results:

**Table (1):** Patient Characteristics Of The Two Studied Groups According To Demographic Data

	Treatment free remission (n = 20)		Dose reduction (n = 20)	
	No.	%	No.	%
<b>Age (years)</b>				
<60	15	75.0	12	60.0
≥60	5	25.0	8	40.0
Min. – Max.	38.0 – 72.0		26.0 – 74.0	
Mean ± SD.	52.20 ± 9.91		53.95 ± 13.46	
Median (IQR)	51.0 (46.0 – 58.50)		55.50(45.50 – 65.50)	
<b>Gender</b>				
Male	13	65.0	13	65.0
Female	7	35.0	7	35.0

In this study, we looked at a single-experience center's with TFR and TKI dose decrease in chronic phase CML patients.

We identified 40 patients who were eligible to participate in our study between 2020 and 2021, who were divided into two equal groups: the first group of twenty patients stopped treatment, and the second group received TKIs therapy with dose de-escalation.

Results showed that 50% (10 patients) of treatment stoppage group relapsed, 9 of them relapsed within the first 6 months while one patient relapsed during the second 6 months, while the group of dose reduction showed 45% relapse (9 patients), 7 of them relapsed within the first 6 months while two patients relapsed during the second 6 months.

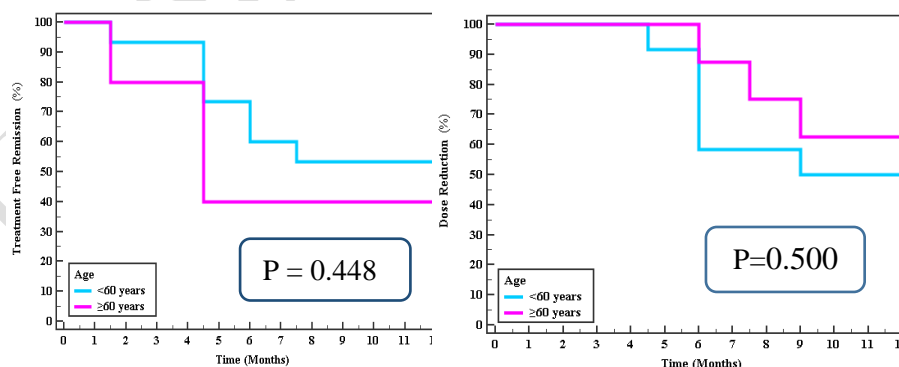
The total relapsed cases (19 patients) regain their deep molecular remission (DMR) or major molecular remission (MMR) after restarting TKI within 1-3 months of the relapse (the same initial TKI).

The relapse was not related (statistically) to age, sex, TKI length, MR period and type of TKI used in treatment free group.

Also the relapse was not related (statistically) to age, sex, MR period and type of TKI used in dose reduction group, but there was a statistically significant difference in duration of the disease in relation to stable molecular remission (duration < 5 years was better than duration  $\geq 5$  years).

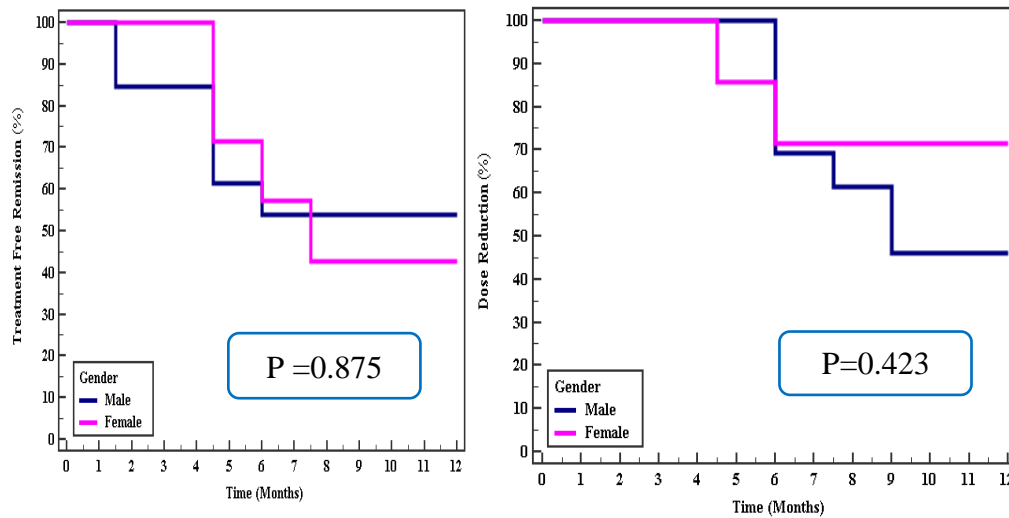
As regards Sokal score and depth of molecular remission (MR) there was a statistically significant difference with predictable variables for maintained remission in both groups.

**Figure 1. Age In Relation To Stable Molecular Remission in both group**



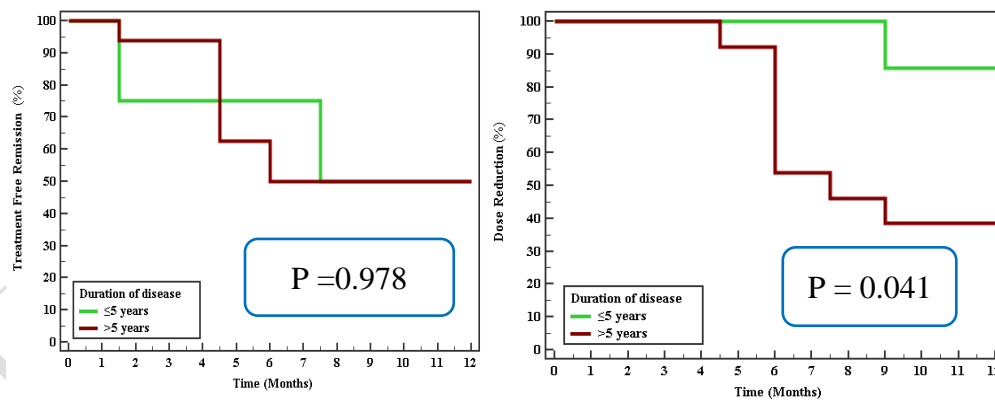
- There was no statistically significant difference in age <60, or  $\geq 60$  in both groups.

➤ **Figure 2. Sex In Relation To Stable Molecular Remission in both groups**



➤ There was no statistically significant difference in sex in both groups.

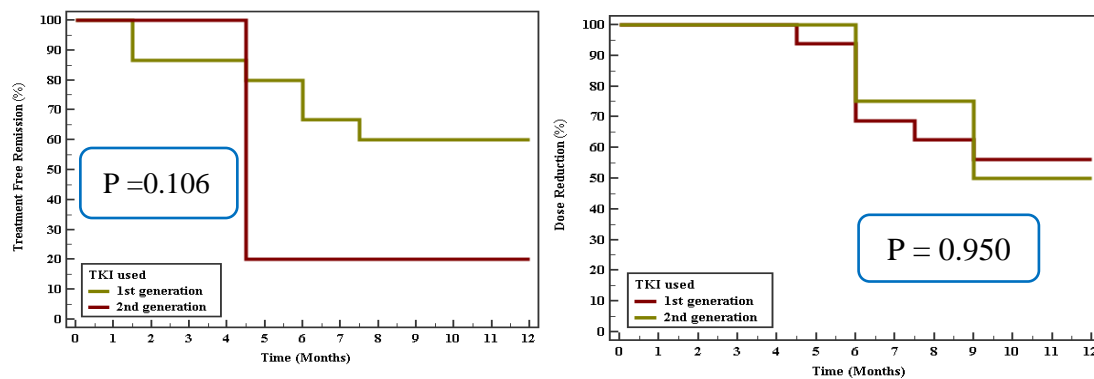
**Figure 3. Duration Of The Disease And TKI Treatment In Relation To Stable Molecular Remission In Both Groups:**



➤ There was no statistically significant difference duration of the disease in relation to stable molecular remission in treatment free group.

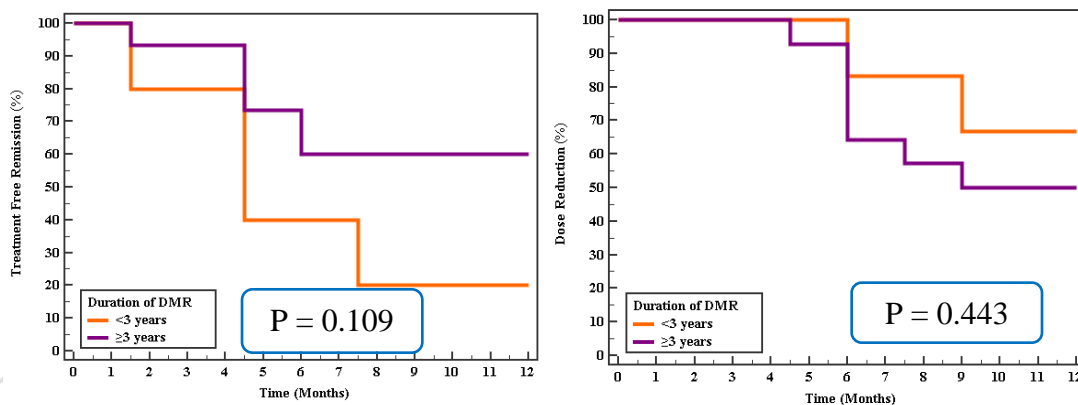
➤ There was statistically significant difference in duration of the disease in relation to stable molecular remission in dose reduction group, duration less than 5 years was better than duration more than 5 years

➤ **Figure 4. Type of TKI used (1st versus 2nd generation) In Relation To Stable Molecular Remission In Both Groups**



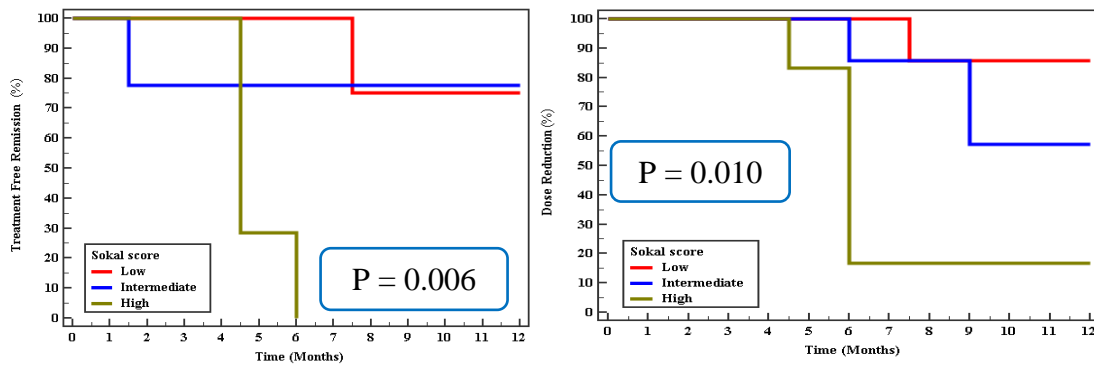
- There was difference between type of TKI used in relation to stable molecular remission in treatment free group, first generation (imatinib) was better than second one (nilotinib), but statistically there is no difference.
- There was no statistically significant difference between type of TKI used in relation to stable molecular remission in dose reduction group.

➤ **Figure 5. Duration of molecular remission In Relation To Stable Molecular Remission In Both Groups:**



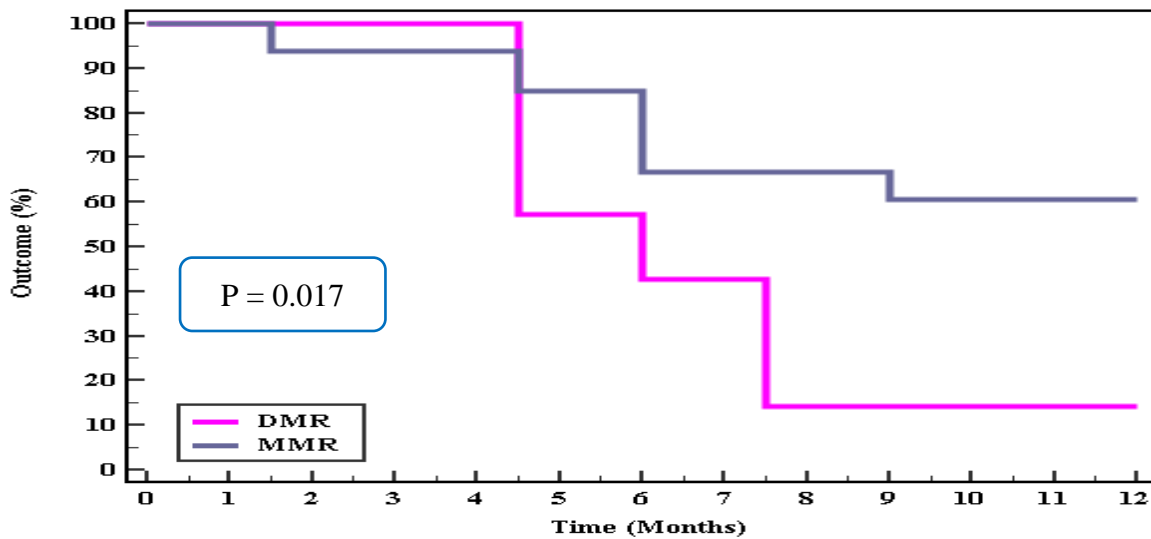
- There was difference between durations of molecular remission, MR more than 3 years was better than less than 3 years in treatment free group (60% vs 20% at the end of the study), but statistically there is no difference.
- There was no statistically significant difference between duration of molecular remission, more or less than 3 years of MR in dose reduction group.

▪ **Figure 6. Sokal score In Relation To Stable Molecular Remission In Both Groups**



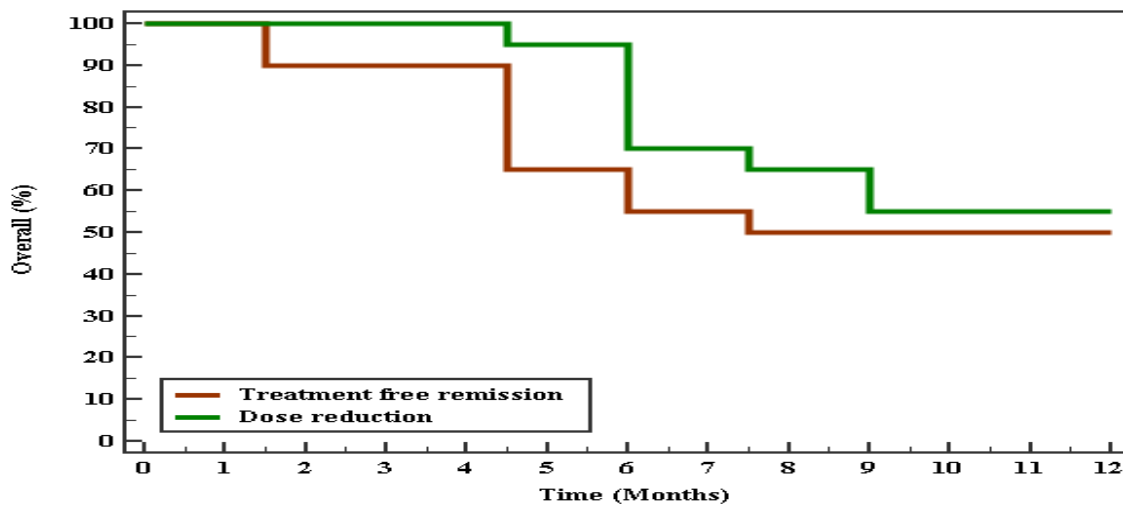
- There was statistically significant difference between low and intermediate sokal score versus high sokal score as regard stable molecular remission in both groups.

**Figure 7. Depth of Molecular response In Relation To Stable Molecular Remission In Both Groups:**



- There was statistically significant difference between MMR versus DMR in both groups regarding stable molecular remission at the end of the study .

**Figure 8. Incidence Of Disease Relapse In Both Groups:**



- There was no statistically significant difference between two groups (treatment free group versus dose reduction group) as regard stable molecular remission and disease relapse .

#### **4. Discussion:**

Treatment of patients with CML is usually initiated when the diagnosis is established. The optimal frontline treatment for patients with chronic-phase CML was the subject of active clinical evaluation but now it is well established to use inhibitors of the BCR/ABL tyrosine kinase (TKIs). Tyrosine kinase inhibitors (TKIs) with greater potency and selectivity than imatinib for BCR/ABL have been evaluated in newly diagnosed patients with CML .

It is therefore possible that none of the currently available TKIs will ultimately translate to a cure, as defined by the absence of all malignant cells. It is, of course, likely that an “operational” cure is achieved whereby most patients who achieve a CMR have very low levels of residual disease, which might not shorten the OS. In an attempt to achieve a conventional cure, many efforts are being directed to develop other treatments, such as immunotherapy and innovative combinations of TKIs and other drugs (As patients with chronic phase (CP)-CML are now having a very long survival and very long follow ups are consequently required before the efficacy of these alternative treatment options could be measured in terms of OS, important surrogate markers as the rates of CCyR, MMR, MR4, and MR4.5 achieved at relevant time points, the more recent parameters of early molecular response (EMR) as well as the more traditional event-free survival (EFS) and progression-

free survival (PFS) parameters have been frequently used as a way to evaluate the relative responses and to compare results. <sup>(207, 208)</sup>

However, in recent years, a variety of clinical studies have explored the option to discontinue or to reduce TKI therapy in patients with sustained deep molecular responses.

Our study discussing the treatment free remission after discontinuation or dose reduction in chronic phase CML patients to assess the validity of this practice and to find any predictors of its success in Egyptian patients.

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Also the relapse was not related (statistically) to age, sex, MR period and type of TKI used in dose reduction group, but There was statistically significant difference in duration of the disease in relation to stable molecular remission ( duration < 5 years was better than duration  $\geq$ 5 years).

As regard Sokal score and depth of MMR there was statistically significant difference with predictable variables for maintained remission in both groups.

So, our study, like others, concluded that the trial to stop or to reduce TKI is a safe and effective maneuver can be tried in selected patients with deep and durable DMR OR MMR with minimal impact on patients' survival or quality of life in addition to financial benefits .

## **5. References :**

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