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Treatment Free Remission Assessment after Discontinuation or dose Reduction of Tyrosine Kinase Inhibitors in Chronic Myeloid Leukemia Patients

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Chronic myeloid leukaemia (CML) is now more than ever the model for targeted treatment in human cancers. The success of imatinib and second-generation tyrosine kinase inhibitors (TKIs) has significantly improved the prognosis of CML patients. Because TKI-treated CML patients have a near-normal life span, two key concerns must be addressed in the future: (1) the treatment's quality of life and ethical implications, and (2) the economic effect of treating patients during their lifespan. One of the most effective methods to examine these two concerns is to ask about quitting TKI in excellent responder patients. Such a technique has now been advocated in multiple studies, and hundreds of patients have formally ceased TKI in clinical trials throughout the world for molecular efficacy.

Aim of the Work: The aim of the present study is to assess:

- Treatment free remission over one year in chronic phase CML patients in deep molecular response for two years or more.
- Quality of life of CML patients and economic factor after treatment discontinuation or dose reduction.

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1. INTRODUCTION

Chronic myelogenous leukaemia (CML) is a clonal illness that is relatively clear to diagnose since more than 95 percent of patients' malignant cells have a particular chromosomal defect known as the Gene mutation (Ph). A bidirectional translocation of the long arms of chromosomes 9 and 22 (t 9; 22) causes the Ph, which may be detected in all hematopoietic progenitors. The Abelson (ABL) oncogene is translocated from chromosome 9 to the breakpoint cluster area of chromosome 22 as a result of this translocation (BCR). This causes the BCR/ABL genes to fuse, resulting in the production of an abnormal tyrosine kinase molecule, which causes the disordered myelopoiesis seen in CML [1].

TKIs which attack the ABL1 tyrosine kinase have shown to enhance CML patients' prognosis. TKI treatment can, in fact, lead to a remarkable molecular remission and a life expectancy equivalent to that of the overall population in the most of CML patients when administered appropriately [2,3].

However the ELN (European Leukemia Network) guidelines for the management of CML suggest that TKI therapy be sustained indefinitely in all responding patients, most recent NCCN (National Comprehensive Cancer Network) guidelines support the view that treatment can be disrupted in a select group of patients, based on the most recent studies on treatment-free remission [2]. Because all TKIs are unable to remove quiescent leukemic stem cells, the vast majority of patients are needed to continue TKI therapy indefinitely, as the majority of patients will relapse if drug is stopped [4].

Nonetheless, patients' quality of life, treatment adherence, and, as a consequence, treatment effectiveness may be impacted by side effects such as persistent, largely mild adverse events. Several clinical discontinuation trials conducted in recent years have shown that 40–60% of chronic phase CML patients (CP-CML) who have obtained a stable deep molecular remission (DMR), defined as a sustained molecular response of at least 4.5($MR^{4.5}$), can stop taking their medication without relapsing [5,6].

A low Sokal risk group upon diagnosis, chronic phase patients, optimal TKI response, extended TKI therapy (> 8 years), and longer DMR (> 2 years) are all connected to a successful treatment-free remission (TFR) [5].

According to all published studies the majority of patients had relapsed within 6 months of quitting TKIs were susceptible to retreatment and achieved at least a major molecular response (MMR) [5,6].

Furthermore, in those who respond well to TKI therapy, reducing the dose can reduce side effects while maintaining a strong molecular response [7].

2. PATIENTS AND 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 Sample Size

40 patients

- 20 patients stopped treatment.
- 20 patient received half the dose of TKIs.

2.2 Study Population

This study was performed on 40 patients in chronic phase CML in deep molecular response for two years or more.

2.3 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. The Shapiro-Wilk test was used to verify the normality of distribution. 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.

2.4 The used Tests were

1 – Kaplan-Meier

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

2 – COX Regression

To estimate the measure of the hazard ratio effect with 95%CI.

3. RESULTS

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 patient relapsed during the second 6 months.

Table 1. Patient Characteristics of the Two Studied Groups According to Demographic Data

	Treatment free remission (n = 20)		Dose reduction (n = 20)	
	No.	**%**	**No.**	**%**
Age (years)				
<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)	
Gender				
Male	13	65.0	13	65.0
Female	7	35.0	7	35.0

Table 2. Distribution of the two studied groups according to different parameters

	Treatment free remission (n = 20)		Dose reduction (n = 20)	
	No.	**%**	**No.**	**%**
Duration disease (years)				
≤5	4	20.0	7	35.0
>5	16	80.0	13	65.0
Min. – Max.	4.0 – 15.0		3.0 – 14.0	
Mean ± SD.	8.65 ± 3.39		7.90 ± 3.65	
Median (IQR)	8.0 (6.0 – 11.50)		6.50 (5.0 – 11.50)	
TKI Period (months)				
Min. – Max.	48.0 – 180.0		36.0 – 168.0	
Mean ± SD.	103.8 ± 40.70		90.60 ± 41.66	
Median (IQR)	96.0 (72.0 – 138.0)		72.0 (60.0 – 120.0)	
TKI used				
1st generation	15	75.0	16	80.0
2nd generation	5	25.0	4	20.0
Length of MR (years)				
Min. – Max.	2.0 – 9.0		2.0 – 10.0	
Mean ± SD.	3.88 ± 1.79		4.20 ± 2.44	
Median (IQR)	3.50 (2.75 – 5.0)		4.0 (2.50 – 4.50)	
Sokal score				
Low	4	20.0	7	35.0
Intermediate	9	45.0	7	35.0
High	7	35.0	6	30.0

The total relapsed cases (19 patiens) 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).

In the treatment-free group, recurrence was not associated (statistically) to age, sex, TKI duration, MR time, or kind of TKI utilised.

In the dosage reduction group, relapse was not associated (statistically) to age, sex, MR period, or kind of TKI used., but There was statistically significant difference in duration of the disease in relation to stable molecular remission (duration < 5 years was better than duration ≥5 years).

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

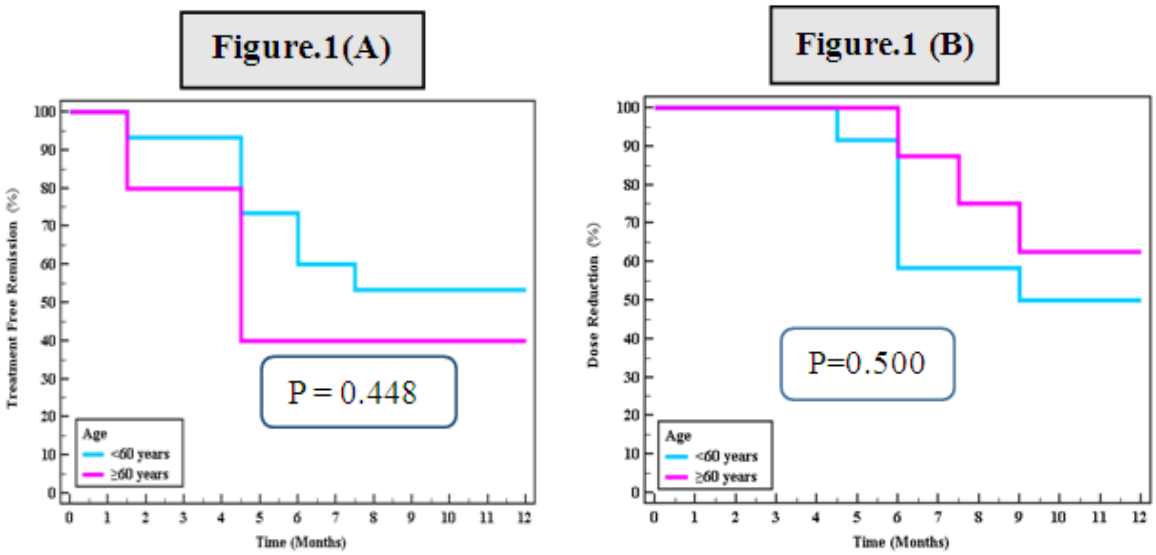

Fig. 1. Age In Relation to Stable Molecular Remission in both group

- *Fig. 1(A). There was no statistically significant difference in age <60,or ≥ 60 in treatment free group.*
- *Fig. 1(B). There was no statistically significant difference in age <60,or ≥ 60 in dose reduction group.*

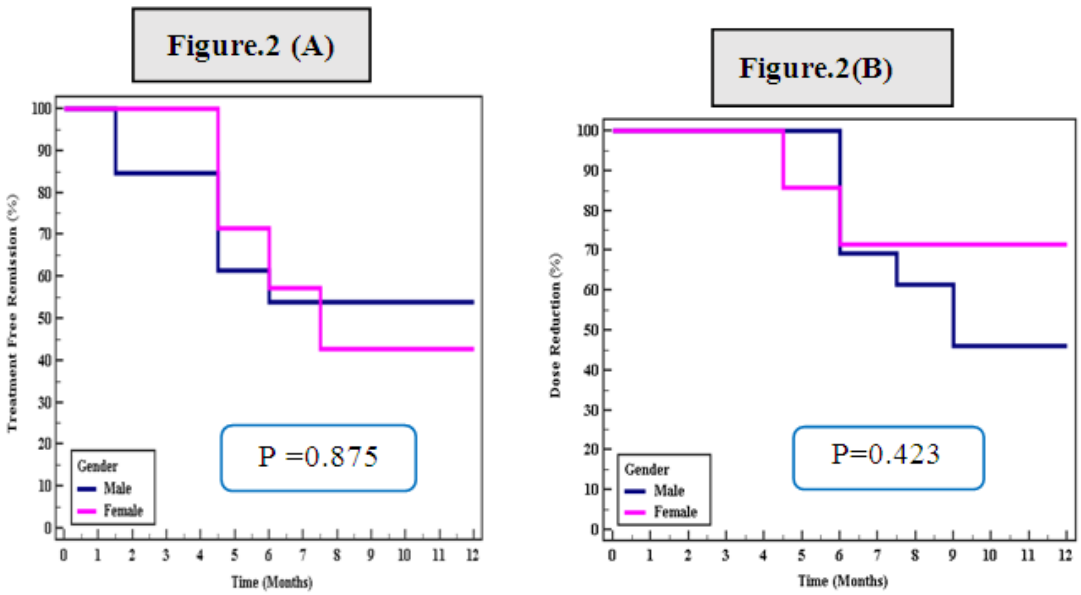

Fig. 2. Sex In Relation to Stable Molecular Remission in both groups

- *Fig. 2(A). There was no statistically significant difference regarding sex in treatment free group.*
- *Fig. 2(B). There was no statistically significant difference regarding sex in dose reduction group*

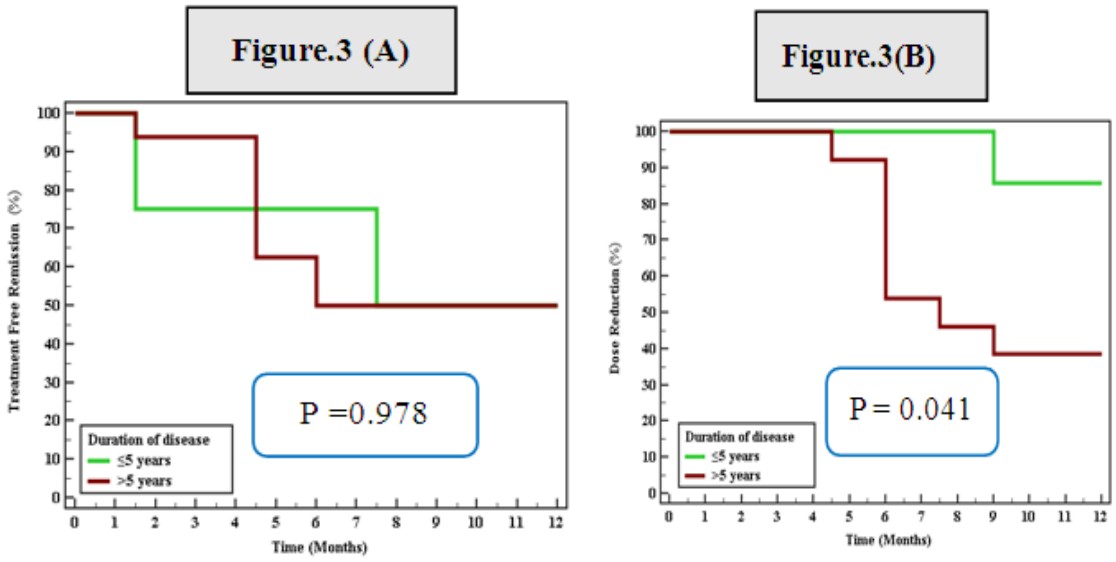

Fig. 3. Duration of the Disease and TKI Treatment In Relation to Stable Molecular Remission in Both Groups

- *Fig. 3 (A). There was no statistically significant difference duration of the disease in relation to stable molecular remission in treatment free group.*
- *Fig. 3 (B). 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*

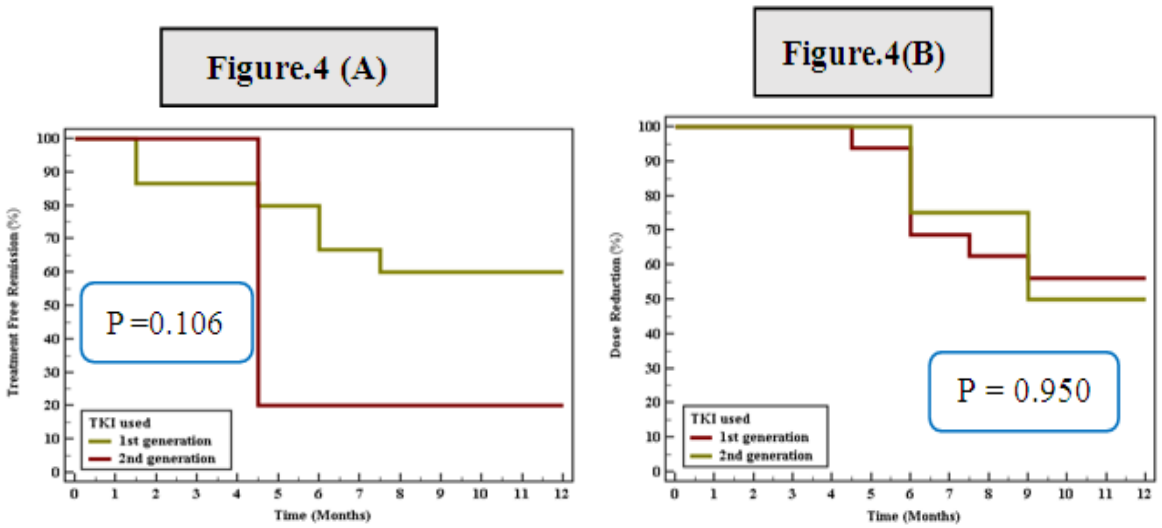

Fig. 4. Type of TKI used (1st versus 2nd generation) in Relation to Stable Molecular Remission in Both Groups

- *Fig. 4(A). 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.*
- *Fig. 4(B). There was no statistically significant difference between type of TKI used in relation to stable molecular remission in dose reduction group.*

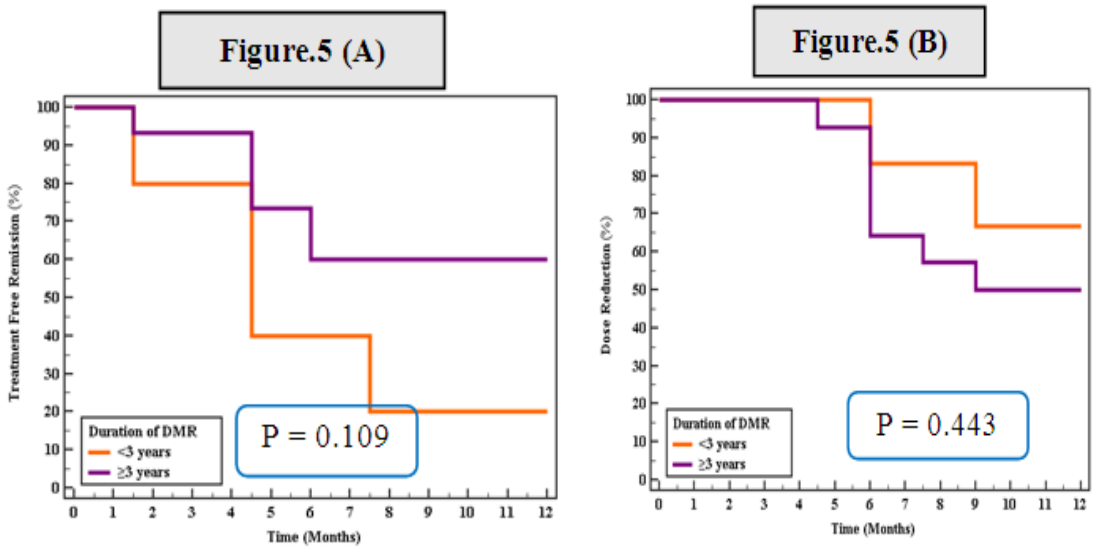

Fig. 5. Duration of molecular remission In Relation to Stable Molecular Remission in Both Groups

- *Fig. 5(A). 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.*
- *Fig. 5(B). There was no statistically significant difference between duration of molecular remission, more or less than 3 years of MR in dose reduction group .*

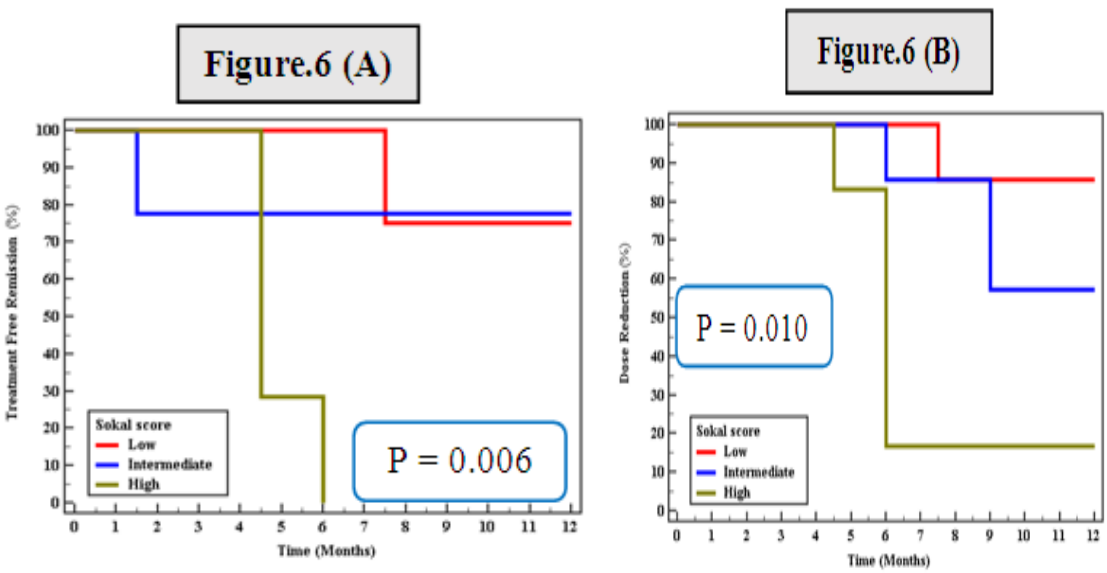

Fig. 6. Sokal score in Relation to Stable Molecular Remission in Both Groups

- *Fig. 6(A). There was statistically significant difference between low and intermediate sokal score versus high sokal score as regard stable molecular remissin in treatment free remission group*
- *Fig. 6(B). There was statistically significant difference between low and intermediate sokal score versus high sokal score as regard stable molecular remissin in dose reduction group*

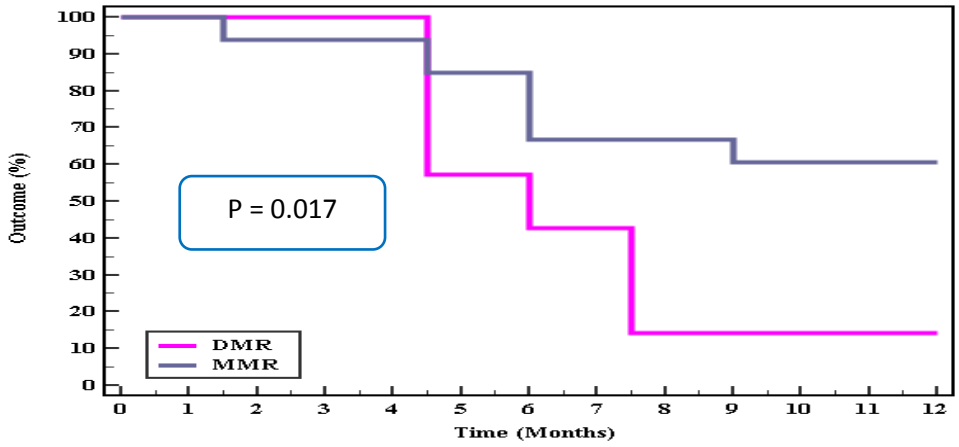

Fig. 7. Depth of Molecular response in Relation to Stable Molecular Remission in Both Groups

➢ *Fig. 7. There was statistically significant difference between MMR versus DMR in both groups regarding stable molecular remission at the end of the study*

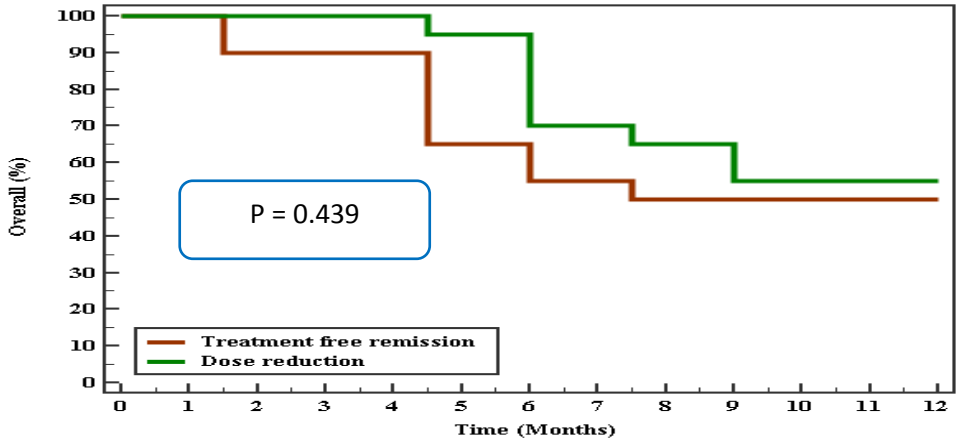

Fig. 8. Incidence of Disease Relapse in Both Groups

➢ *Fig. 8. There was no statistically significant difference between two groups (treatmen free group versus dose reduction group) as regard stable molecular remission and disease relapse*

Table 3. COX regression analysis for the parameters affecting progression outcome from remission

	HR (LL_UL 95%C.I)	
	Dose reduction group (n = 9 vs. 11)	**Treatment free remission (n = 10 vs. 10)**
Age (<60 years)	1.551 (0.387 – 6.218)	0.618 (0.159 – 2.405)
Male	1.802 (0.374 – 8.695)	0.910 (0.257 – 3.228)
Duration of disease (>5 years)	5.958 (0.737 – 48.189)	0 .980 (0.207 – 4.642)
TKI used		
1st generation	0.954 (0.198 – 4.596)	0.383 (0.102 – 1.434)
2nd generation	1.048 (0.218 – 5.046)	2.611 (0.697 – 9.771)
Duration of DMR (≥3 years)	1.758 (0.364 – 8.487)	0.396 (0.111 – 1.412)
Sokal score		
Low®	1.000	1.000
Intermediate	3.083 (0.321 – 29.656)	1.109 (0.100 – 12.234)
High	11.520 (1.273 – 104.251)	8.637 (0.881 – 84.692)

HR: Hazard ratio; C.I: Confidence interval; LL: Lower limit; UL: Upper Limit

4. DISCUSSION

CML is hypothesised to be caused by a genetic alteration that occurs in a pluripotent hematopoietic stem cell. This genetic mutation causes a balanced translocation across chromosomes 9 and 22, t (9; 22) (q34; q11), in the majority of patients; the resultant 22q- chromosome is termed as the Philadelphia (Ph) chromosome [8].

The finding that excessive kinase activity might be suppressed in a very targeted manner in the mid-1990s was a major breakthrough in the treatment of CML [9].

Imatinib (Gleevic TM) was unexpectedly approved for first-line treatment of CML patients in May 2001. Imatinib significantly lowers the amount of leukaemia cells in a patient's body, and by 2003, it had shown promise in terms of prolonging survival when compared to earlier therapy. Since then, the drug's unrivalled clinical success has been validated. It has a significant impact on CML's natural history and overall prognosis [10].

Innovative approaches to reinstate ABL1 tyrosine kinase suppression have therefore been the focus of efforts, but not completely. Some of these efforts resulted in the creation of alternative inhibitors of ABL1 protein kinase, second- or next-generation TKIs, which have since been proven to be effective. Dual kinase inhibitors, like dasatinib and bosutinib, differ from imatinib in that they target numerous additional kinases, including SRC, in addition to the ABL1 kinase, and medications like nilotinib, an enhanced form of imatinib, are among these treatments. The pan-BCR–ABL1 inhibitor ponatinib, commonly known as a third-generation TKI, has just been introduced to these agents [11].

As a result, it's probable that none of the TKIs now available will lead to a cure, as described by the lack of all malignant cells. Of course, a "operational" cure is likely to be achieved, in which most patients who obtain a CMR have very low levels of residual illness, which may not shorten the OS. Many efforts are being made on developing new therapies, such as immunotherapy and novel combos of TKIs and other medicines, in order to reach a conventional cure (Because patients with chronic phase (CP)-CML now have very long survival times, long follow-ups are needed before the efficacy of these alternative treatment options can be measured in terms of OS. Important surrogate markers such as the rates of CCyR, MMR, MR4, and MR4.5 achieved at relevant points of time, the more latest parameters of early molecular response (EMR), as well as more conventional event-free survival (EFS) and progression-free survival (PFS), as well [12].

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.

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

We found 40 patients eligible to join our study during years 2020 and 2021, classified into two groups ,first group of twenty patients stopped treatment and the second one received TKIs therapy with dose de-escalation. In contrast to previous research on the same topic, this is a reasonable amount. For example, the first published pilot research comprised just 12 participants [13], followed by the "Stop Imatinib" (STIM) trial, which included 100 patients [14].

A statewide survey in Japan discovered 50 individuals who had been off imatinib for at least 6 months, 43 of whom were evaluated, while the TWISTER trial saw approximately the same number of patients (40 patients) [15].

Our data mirrors the European Stop Kinase Inhibitor (EURO-SKI) experiment, which demonstrated male preponderance (58.5 percent of patients) [16], but it contrasts from the TWISTER study, which included only 37 percent males.

The median age of the study population was 51 years for treatment free group, while for dose reduction group the median age was 55. The median age of patients in the STIM trial was 63 years (range 29-80) [17], 61 years in the STIM 2 study, 58 years in the TWISTER study [15], and 53.3 years in the EURO-SKI study [18].

All studied patients were in DMR OR MMR for at least 2 years before stopping the TKI like all other studies discussing TFR or dose reduction [14,15,17,18].

In our study the minimum period for TKIs before stoppage or dose reduction was 36 month, as in TWISTER study, EURO-SKI study, STIM 1 study and UK DESTINY study [14,15,17,18]. 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, This was also shown in the STIM study, where the majority of relapses occurred in the first 7 months (58 of 61), [14], in STIM 2 (45 of 48 cases), [19], and in TWISTER, where 15 of 22 relapses occurred in the first 6 months [15].

The group of dose reduction showed 45 % relapse (9 patients), 7 of them relapsed within the first 6 months while two patient relapsed during the second 6 months.

The total relapsed cases (19 patiens) regain their DMR or MMR after restarting TKI within 1-3 months of the relapse (the same initial TKI). In the STIM study, 56 (of 61) patients reached their MMR following re-imatinib in a median of four months [16], and this was also found in the STIM 2 trial in all relapsed patients within four months of re-imatinib [19].

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 statistically significant difference in duration of the disease in relation to stable molecular remission (duration < 5 years was better than duration ≥5 years).

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

5. CONCLUSIONS AND RECOMMENDATIONS

- Our study, like others, found that stopping or reducing TKI is a safe and successful technique that may be undertaken in chosen patients with deep and lasting DMR OR MMR with low influence on survival or quality of life, as well as financial advantages. In adult CML patients in the chronic phase with stable DMR or MMR for at least two years, stopping or reducing TKI therapy is a beneficial strategy. To reduce the treatment toxicities (both medical and financial), such practises should be advocated for all eligible patients, especially in our nation and other poor countries. Precise patient selection resulted in better outcomes and a longer period of remission. There is a greater need for improved documentation and stringent follow-up of CML patients, particularly those who want to discontinue taking their medication. CML is a treatable condition that may be halted without causing harm to the patient's health. Finally, more research is needed to enhance patients' criteria for TKI discontinuation or de-escalation.

CONSENT

Informed consent was obtained from all patients involved in this study.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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