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Treatment-free remission in Chronic Myeloid Leukemia (CML): experience of Basrah haematology centre

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SUMMARY

Improved survival rates in Chronic Myeloid Leukaemia (CML) lead to increasing prevalence of the disease, increasing cost and burden on health care systems. The current study aimed to assess the outcome of CML patients that maintained a durable molecular response, after TKI stopping in Iraq. The study enrolled 18 patients with CML who were treated for more than 5 years with Tyrosine Kinase Inhibitors (TKIs) and got a Major Molecular Response (MMR) for 2 years. All patients were subjected to close follow-up after stopping TKI with PCR every 3 months to monitor molecular response. The median age of 45-year, median duration of disease before stopping TKI was the 93-month and the median duration of MMR was 37-month. During a median duration of 24 months of follow-up after TKI stopping, 13 patients (72%) succeeded to maintain MMR, while 5 patients (28%) did not. The molecular relapse occurred during the first year of follow up and all 5 patients succeeded to reach MMR (bcr-abl ≤ 0.1%) 3 months after resuming TKI. There was no significant impact of age and duration of treatment and MMR before TKI stopped on treatment-free remission. Treatment-free remission for at least 2 years was found among 70% of the studied patients. Molecular relapses typically occurred within 12 months of TKI discontinuation, and patients quickly regained their molecular response upon retreatment with the same TKI.

Key words: CML, molecular response, Treatment-free remission, TKI

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INTRODUCTION

Chronic Myeloid Leukaemia (CML) is a haematological malignancy characterized by the presence of the BCR-ABL oncogene (BCR: breakpoint cluster region gene, ABL: Abelson proto-oncogene), which is the result of a reciprocal translocation between chromosomes 9 and 22 t (9;22), in a hematopoietic stem cell [1]. Tyrosine Kinase Inhibitors (TKIs) imatinib, nilotinib, and dasatinib are the first-line treatment. Clinical response to treatment is assessed initially by monitoring the reduction of the white blood cell count in peripheral blood, while the molecular response is assessed by measurement of BCR-ABL transcript levels against a control gene [2]. There are different stages of molecular response, including early molecular response (BCR-ABL ≤ 10% at 3 months), major molecular response (MMR; BCR-ABL ≤ 0.1%), and deep molecular responses, such as MR 4 (BCR-ABL ≤ 0.01%) and MR 4.5 (BCR-ABL ≤ 0.0032%). Responses beyond MR 4.5 are often undetectable by conventional RQ-PCR. [3].

Improved survival rates in CML lead to increasing prevalence of the disease, and so, increasing cost and burden on health care systems [4]. Moreover, TKIs are associated with many adverse effects, including fatigue, nausea, depression, sleep disturbances, diarrhoea, pain, fluid retention, and skin problems [5]. Of note, some deleterious side effects have been recognized with longer follow-up, for example, pulmonary hypertension in patients on dasatinib [6] and peripheral arterial occlusive disease in patients on nilotinib [7]. All of that makes the idea of stopping TKI after achieving a molecular response an appealing one.

Initially, several studies from Europe and Australia suggested the safety of stopping TKIs with regular monitoring [8-13]. In these studies, 22%-61% of patients with CML in a TKI-induced major molecular response maintained this response after stopping of TKIs, and all patients with molecular relapse could respond to retreatment with TKI.

This study aimed to assess the outcome of CML patients that maintained a durable molecular response, after TKI stopping.

METHODOLOGY

This retrospective study was conducted at Basrah Center for Oncology and Hematology in September 2020. It included analysis of 18 patients with chronic myeloid leukaemia, by reviewing their clinical data already documented in their files.

Tab. 1. Characteristics of the studied group

Patient characteristic		No.
Gender	male	8
	female	10
Median age (Range)		45.5 (38-73 yr)
The median duration of TKI therapy		93
The median duration of DMR		37.5
TKI at time of TFR trial	Imatinib (1st line)	15
	Nilotinib (2nd line)	3

Tab. 2. Comparing variables of sustained and unsustained groups

Variable	Sustained group	Unsustained group	P-value
Number (%)	13 (72%)	5 (28%)	-
Median age	45 yr	46 yr	0.17
Median TKI therapy duration	92 month	96 month	0.12
Median DMR duration	37 month	39 month	0.2

All these patients were subjected to the TFR trial according to a local guideline after meeting the following criteria:

- The whole duration of treatment should not be less than 5 years
- The whole duration of Deep Molecular Response (DMR) (BCR-ABL ≤ 0.01%) within these 5 years should not be less than 2 years
- Written consent from all patients subjected to this trial

Neither the initial risk score nor the initial kind of TKI used was considered before subjecting patients to this trial. After stopping TKI, those patients were followed monthly by complete blood count, and every 3 months by PCR during the 1st year and every 6 months thereafter. During the follow-up period, any patient with detected loss of MMR, i.e. BCR-ABL >0.1%, was quitted from the trial and retreated with TKI. Patients who succeeded to maintain molecular remission during the follow-up period were called "sustained group", while those who showed molecular relapse were called "unsustained group".

The study including the protocol and intervention procedures was approved by the Medicine Ethical Committee of the Iraqi Board for Medical Specialization and followed the principles of the revised declaration of Helsinki.

Assessment of BCR-ABL

Enrolled patients had their blood been drawn for Real-Time Quantitative Polymerase Chain Reaction (RQ-PCR) at a reference laboratory, using Gene Xpert, by which DNA was extracted and amplified inside a closed system (cartridge). Quantitative results were first normalized against a reference gene such as ABL. Subsequently, results were converted to an International Scale (IS) that harmonized reporting of the molecular response.

Statistical analysis

IBM SPSS Statistics 19 program was used for statistical analysis. A p-value of less than 0.05 was regarded as significant. Student t-test was used to compare between means.

RESULTS

This study enrolled 18 patients who met the criteria for the TFR trial, 8 males and 10 females. The median age for the studied group was 45.5 yr. Before TKI stopped, the median duration of TKI therapy was 93 months, and the median duration of DMR was 37.5 months. On-time of TKI therapy stopping, three patients were on nilotinib as a 2nd line therapy, while the rest were on imatinib as a 1st line therapy (Table 1).

During a median duration of 24 months of follow-up after TKI stopping, 13 patients (72%) succeeded to maintain molecular remission (sustained group), while 5 patients (28%) did not (unsustained group).

Among the unsustained group, the molecular relapse (BCR-ABL>0.1%) occurred 3 months after TKI stopping for 1 patient, 6 months for another, and 12 months for the 3 other patients. Four patients were on imatinib as 1st line therapy at the time of TKI stopping, while only 1 patient was on nilotinib as 2nd line therapy. Before TKI stopped, the median duration of treatment was 96 months, and the median duration of DMR was 39 months. Fortunately, all these 5 patients succeeded to reach MMR (bcr-abl ≤ 0.1%) 3 months after resuming TKI.

Among the sustained group, 2 patients were on nilotinib as a 2nd line therapy on time of TKI stopping, while 11 patients were on imatinib as a 1st line therapy. Before this trial, the median duration of treatment was 92 months, and the median duration on DMR was 37 months.

By comparing these variables in the 2 groups, the differences were statistically not significant (Table 2).

DISCUSSION

In this study, we retrospectively investigated the outcomes of patients after TKI discontinuation. Our study showed that in 13 of 18 patients (72%) TFR could be maintained at the time of analysis with a median period of 24 months, and all the relapses occurred within the 1st year of follow-up. Luckily, all 5 patients who experienced molecular relapse, were successfully re-entered into MMR 3 months after re-treatment with TKIs.

Several studies have investigated TFR following long-term TKI

therapy [9, 10, 14-16]. In two studies, approximately 40% of patients were able to maintain molecular remission for >3 years, and most molecular relapses occurred during the first 6 months after TKI stopping [10, 14]. Another study showed that 71.4% of patients had sustained TFR at a median time of analysis of 32.1 months, and the relapsing resumed treatment after a median of 5 months. Fortunately, all of them re-achieved molecular remission within a median of 3 months after TKI therapy was re-commenced [15].

However, in previous studies, two patients experienced progression to accelerated phase [16] and lymphoid blast crisis [9] after TKI discontinuation.

A variety of factors have been identified as potentially predictive of successful TFR [17-19]. In STIM1, patients with low and intermediate Sokal risk and those with a longer duration of imatinib therapy were more likely to maintain TFR [17]. Similarly, in EUROSKI, treatment and molecular response duration were predictive of TFR success [18]. In DADI, no association was found between the duration of prior TKI therapy and successful TFR, although higher rates of TFR at 12 months were observed in patients who demonstrated an increased number of Natural Killer (NK) cells in the peripheral blood during the consolidation phase before discontinuation [19]. In our study, no significant impact of age and duration of treatment and DMR before TKI stopping on TFR success was observed. However, a larger sample size is required for more reliable statistical analysis.

CONCLUSION

Approximately 70% of patients with CML who achieved sustained (≥ 2 years) DMR with TKI therapy could achieve TFR. Molecular relapses typically occurred within 12 months of TKI discontinuation, and patients quickly regained their molecular response upon retreatment with the same TKI.

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