Clinical Paper

Response to Therapy, Treatment Intolerance and Tyrosine Kinase Inhibitor Cessation Eligibility in a Real-World Cohort of Chronic Myeloid Leukaemia Patients.

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ABSTRACT

Tyrosine kinase inhibitor (TKI) therapy has revolutionised chronic myeloid leukaemia (CML) management, it is however associated with significant side effects and economic burden. Recent studies have demonstrated that treatment free remission is possible in certain patients.

The aim of this study was to characterise a real-world population in terms of response to therapy, treatment intolerance and potential eligibility for stopping treatment.

Included were 105 CML patients diagnosed in Northern Ireland from March 2009-February 2018. Response to treatment was defined as per the 2009 and 2013 European Leukaemia Net guidelines. Potential for treatment cessation was assessed as per the 2017 UK Interim Expert Opinion on Discontinuing Tyrosine Kinase Inhibitor Treatment in Clinical Practice for Treatment-Free Remission in Chronic Myeloid Leukaemia.

Our cytogenetic data cohort had a 12-month complete cytogenetic response rate of 66% and the molecular data cohort had a 12-month major molecular response rate of 38%. Of those commenced on 2nd line TKI therapy 81% achieved an optimal response at 12 months. Twenty-two patients developed intolerance and required a change in TKI therapy. The commonest side effects were gastro-intestinal upset (18%), transaminitis (16%) and fluid retention (16%). In our cohort, 20% were considered eligible to stop TKI therapy. The commonest reason for ineligibility was insufficient duration of therapy (25%).

We observed that 1st and 2nd line TKI therapy are effective but problems with failure and intolerance persist. Additionally, this study identifies a cohort of patients who may attempt TKI cessation using the UK Interim Expert Opinion report on TKI therapy discontinuation.

BACKGROUND

Chronic myeloid leukaemia (CML) is a myeloproliferative neoplasm with a reported incidence of 1-2 cases per 100,000 adults [1]. CML typically has three stages; chronic phase (CP), accelerated phase (AP) and blast phase (BP). As the disease progresses, cytogenetic abnormalities accrue, accompanied by symptomatic deterioration. The majority of patients are diagnosed during CP and most evolve into AP before BP. However, 20% of patients transit into an acute blastic process without AP warning signals [2].

Central to the pathogenesis of CML is the formation of the constitutively active tyrosine kinase, BCR-ABL1. This oncoprotein plays a key role in leukemogenesis by stimulating growth and replication by the manipulation of downstream signalling pathways and by generating a cytokine-independent cell cycle with aberrant apoptotic signals [3].

Identification of this critical pathway led to the development of targeted drug therapy, tyrosine kinase inhibitors (TKIs), which interfere with the interaction between BCR-ABL1 and adenosine triphosphate, thereby preventing proliferation of the malignant clone.

The IRIS trial was a seminal study confirming the significance of TKIs and led to the study drug, imatinib, being approved for first line treatment [4]. TKIs have improved the 10-year overall survival from approximately 20% to 80–90% [5]. A recent study by Bower *et al*. demonstrated that the life expectancy of CML patients is approaching that of the general population [6].

Despite this, long term TKI therapy is associated with a heavy economic burden which will increase as CML becomes more prevalent due to improved survival [7]. Furthermore, patients are frequently affected by significant and occasionally lethal side effects. Several studies have indicated that approximately half of patients who achieve a deep and sustained molecular

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response can safely and successfully stop TKI therapy and obtain treatment free remission (TFR) [8].

In patients with a molecular recurrence necessitating resumption of TKI therapy, the overwhelming majority retained their sensitivity to TKI therapy. In all major published trials to date, only one case has been identified where a patient progressed to BP despite therapy recommencement [9].

Although numerous trials have confirmed the safety and efficacy of TKIs, assessment of their real-world effectiveness and tolerance in a general CML population is scarce. Furthermore, identifying patients who may attempt to gain TFR is a relatively novel strategy.

The aim of this study was to provide a detailed description of the presentation and management of a real-world sample of CML patients. We sought to assess the effectiveness and tolerance of TKI therapy and evaluate what proportion of participants were deemed eligible to stop TKI therapy in an attempt to obtain TFR.

METHODS

This study included 105 CML patients diagnosed from March 2009 to February 2018 and managed by the Belfast City Hospital Haematology Department. This cohort was identified by interrogation of Consultant patient records. Patients not managed by this tertiary centre were not included. Data was collected using patient medical notes and electronic laboratory records.

Table 1:

Baseline Characteristics of the Study Population

Characteristic	Study Population
Number of Patients	105
Median Age (range)- years	61.5 (4-94)
Male sex- no. (%)	62 (59)
Palpable splenomegaly no. (%)	50 (48)
Median haemoglobin for males (range)- g/l	118.5 (67-155)
Median haemoglobin for females (range)- g/l	110 (64-148)
Median platelet count (range)- x10^9/l	96.8 (13.4-563)
Median white cell count (range)- x10^9/l	340 (84-2507)
EUTOS risk group-no. (%)	
Low	89 (85)
High	5 (5)
Unknown	11 (10)
Phase- no. (%)	
Chronic	99 (94)
Unknown	6 (6)

Cytogenetic analysis and BCR-ABL1 transcript analysis were performed at a single centre (Haematology Laboratory, Belfast City Hospital). Transcript analysis was conducted using quantitative polymerase chain reaction technology.

Results for response to treatment were expressed as per the 2009 and 2013 European Leukaemia Net (ELN) guidelines and applied retrospectively, depending on the date of diagnosis [10,11]. Potential for treatment discontinuation was assessed as per the eligibility criteria expressed by the 2017 UK Interim Expert Opinion on Discontinuing Tyrosine Kinase Inhibitor Treatment in Clinical Practice for Treatment-Free Remission in Chronic Myeloid Leukaemia [12].

Data were analysed using descriptive statistics and IBM SPSS® software was used.

RESULTS

Presenting Features

This study included 105 patients (62 males, 43 females) with a median age at diagnosis of 61.5 years. Baseline characteristics are shown in Table 1. The most common presenting symptoms were fatigue (32%), unintentional weight loss (24%) and night sweats (17%). 30% of patients were diagnosed as a result of an incidental finding. At diagnosis the majority of males and females were anaemic, 77% and 63% respectively. Moreover, 38% of patients were thrombocythaemic and 7% were thrombocytopenic.

Treatment and Response to Therapy

The majority of patients (74%) did not receive cyto-reduction prior to TKI initiation. However, 23% did receive hydroxycarbamide and 3% underwent leucopheresis. The most commonly prescribed 1st line TKI was imatinib (81%) with the remainder receiving 2nd generation TKI therapy, namely nilotinib (12%) and dasatinib (7%).

The response to 1st line TKI therapy was assessed, using cytogenetic data, in 57 patients in accordance with the 2009 ELN guidelines [10]. Cytogenetic data was not always available because of a lack of bone marrow biopsy data, probably arising from clinician reluctance to subject patients to an invasive procedure, especially if symptoms had resolved along with a downward trending *BCR-ABL1* transcript level. See Table 2 for availability at the various timepoints. In those with cytogenetic data available 79%, 72% and 66% achieved an optimal response to therapy at 3, 6 and 12 months respectively (Table 2). Whereas, 14%, 12%, and 6% of patients were determined to have a failure response to therapy.

The response to 1st line TKI therapy was assessed, using molecular data, in 47 patients in accordance with the 2013 ELN guidelines [11]. Due to a lack of compulsory monitoring molecular data was not always available (Table 3). In those with molecular data available, 50%, 43% and 38% achieved an optimal response to therapy at 3, 6 and 12 months respectively (Table 3). However, 9%, 22% and 15% of patients were determined to have a failure response to therapy.

TABLE 2:

Response to 1st Line TKI Therapy as Defined by the 2009 ELN Guidelines

	Response to Therapy						
	Optimal	Suboptimal	Failure	Unknown	Deceased	No Bone Marrow Biopsy	2nd Line Therapy Commenced
3 Months	11	1	2	2	1	40	0
6 Months	18	3	3	1	1	30	1
12 Months	23	7	2	2	1	19	3

TABLE 3:

Response to 1st Line TKI Therapy as Defined by the 2013 ELN Guidelines

	Response to Therapy						
	Optimal	Warning	Failure	Unknown	Deceased	Awaited	2nd Line Therapy Commenced
3 Months	17	14	3	9	1	3	0
6 Months	16	12	8	6	1	3	1
12 Months	15	11	6	4	1	3	7

TABLE 4:

Response to 2nd Line TKI Therapy as Defined by the 2013 ELN Guidelines

	Response to Therapy					
	Optimal	Warning or Failure	Unknown	Deceased	Awaited	3rd Line Therapy Commenced
3 Months	14	4	9	0	1	0
6 Months	18	3	5	1	1	0
12 Months	14	6	3	2	2	1

Monitoring was much more stringent in this cohort due to the less invasive sampling required for transcript analysis.

A total of 28 patients required a change in TKI therapy due to an inadequate cytogenetic and or molecular response. Subsequently, they were commenced on 2nd line therapy in an attempt to obtain disease control and to prevent progression. These patients were assessed for an optimal response to 2nd line therapy as defined by the 2013 ELN guidelines [11]. In those with molecular data available, 78%, 86% and 81% achieved an optimal response at 3, 6 and 12 months respectively (Table 4).

Treatment Intolerance

Initial TKI therapy was changed in 47% of patients due to inadequate response (26%), treatment intolerance (18%) and study completion (3%). Throughout their entire treatment regime 22 patients were identified who due to intolerance required a change in therapy. Among these 22 patients there were 38 instances of a change in TKI therapy, thereby highlighting that several patients experienced intolerable side effects to more than one agent. The most common side effects resulting in a change in therapy were gastrointestinal upset (18%), transaminitis (16%) and fluid retention (16%) (Figure 1).

Eligibility for TKI Discontinuation

The cohort of patients was assessed for eligibility to stop TKI therapy in accordance with a recently published UK Interim Expert Opinion on TKI discontinuation [12]. This report advises that TKI discontinuation may be attempted in adult patients with no prior history of AP or BP disease. Moreover, the patient must have been on TKI therapy for at least 3 years and have had a sustained response i.e. (*BCR-ABL1* ≤0.01%) throughout the last 2 years prior to attempted discontinuation[12].

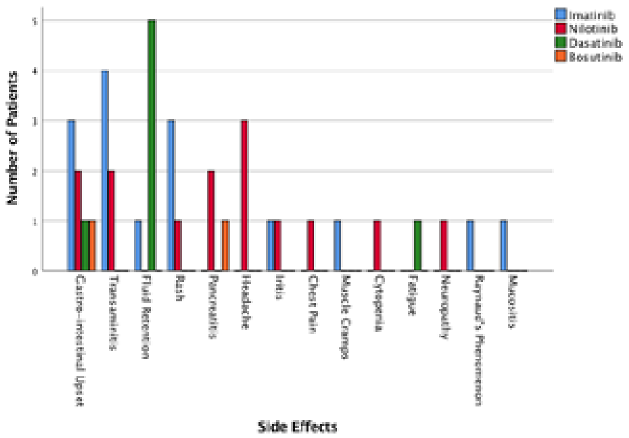

Fig 1; Side Effects Associated with Tyrosine Kinase Inhibitor Therapy Resulting In a Change in Therapy

In this cohort 20% were considered eligible to stop TKI therapy in an attempt to obtain TFR. Reasons for ineligibility included insufficient duration of therapy (25%), history of inadequate response to therapy (16%) and a *BCR-ABL1* transcript level ≥ 0.01 within the past 2 years (16%) (Figure 2).

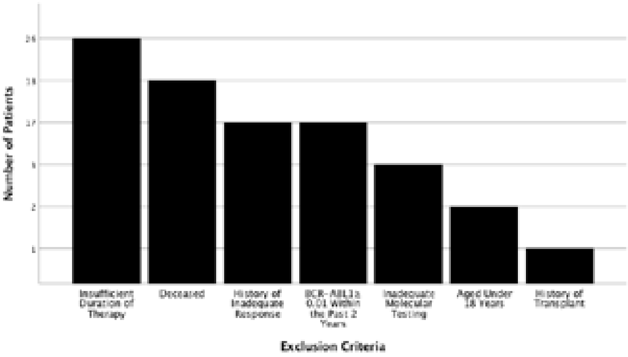

Fig 2. Reasons for Failure to Meet Eligibility Criteria as Defined by the 2017 UK Interim Expert Opinion on Discontinuing Tyrosine Kinase Inhibitor Treatment in Clinical Practice for Treatment Free Remission in Chronic Myeloid Leukaemia

Follow Up

This population of patients were followed up until March 2018. During follow up 18 out of 105 patients died, however, only 1 death was attributable to a CML blast crisis. One patient died from complications of a bone marrow transplant and a further patient died from acute liver failure attributed to imatinib therapy. Other common causes of death included sepsis and solid malignancy.

Annual *BCR-ABL1* transcript levels were assessed to determine what proportion of patients achieved a major molecular response (MMR). MMR is defined as a 3-log reduction in transcript levels from the standardised baseline or a transcript level of <0.1 in the International Scale [13].

Data suggests that the proportion of patients achieving and maintaining a MMR increases as time passes. Molecular follow up data at 2 years revealed that 63% achieved a MMR, at 5 years 83% achieved a MMR and at 8 years 100% of patients, still alive, had achieved a MMR. At the time of data analysis 8 patients had reached 8 years of follow up; all of whom had achieved a MMR.

DISCUSSION

Real-world data has important implications that inform clinical practice. The aim of this study was to provide such data on the presentation, management and outcomes of a CML population. We sought to highlight issues with treatment failure and intolerance and to identify a cohort of patients, using recently published guidance, who could stop therapy in an attempt to obtain TFR.

Advances in the understanding of the pathophysiology of CML have led to the development of targeted therapy which has changed management. However, a substantial number of patients suffer significant intolerance to TKI therapy. In this study 21% of patients experienced intolerance to one or more TKIs, necessitating a change in therapy. Side effects such as gastro-intestinal upset and transaminitis were common across the entire class of drugs. Certain characteristic side effects were coupled with particular TKIs as demonstrated by the relationship between dasatinib therapy and pleural effusions. It is essential that the clinician adopts a proactive stratagem to manage side effects. The association of side effect burden and poor medication adherence with a suboptimal disease response demands that side effects are managed aggressively. With unmanageable side effects it is appropriate to switch TKI therapy and with 3rd generation TKIs filtering into clinical practice, this will promote the therapeutic armoury available [14]. Our results mirror other real-world studies which have demonstrated that 41-44% of patients change TKI therapy due to treatment intolerance or failure [15,16].

Furthermore, TKI therapy is associated with substantial financial implications. As the life expectancy of CML patients now approaches that of the general population, the provision of life long therapy is expensive [6]. Consequently, TFR is an attractive therapeutic target for the health service. Analysis by Padula *et al*, suggests that the annual cost of imatinib therapy per patient in the United States was almost $80,000 per year and introduction of generic imatinib resulted in only a modest decrease in cost [17]. Therefore, safely stopping TKI therapy represents a substantial cost saving. However, it must be remembered that achievement of TFR will have its own unique costs. Patients will require closer monitoring and there is an argument for indefinite *BCR-ABL1* transcript analysis to safe guard against a delayed diagnosis of disease relapse and to help inform clinical practice regarding the long-term durability of TFR. Regardless, the standard cost of performing a transcript assay in our unit is £200, therefore, compared to one year of TKI therapy, regular molecular monitoring remains highly cost effective.

Our cytogenetic data cohort had a 12-month complete cytogenetic response (CCyR) rate of 66% and the molecular data cohort had a 12-month MMR rate of 38%; comparable to other population-based registries [15,18,19]. The EUTOS registry, one of the largest CML population-based registries, had a 12-month CCyR rate of 57% and a MMR rate of 41% [19]. Interestingly, our results compare favourably to Lucas *et al*., who using a surrogate end point CCyR equivalence (CCRe) which combined molecular expression data and cytogenetic data, revealed a 12-month CCyR equivalence rate of approximately 41% within a real-world UK population of CML patients treated with imatinib [20]. However, a proportion of patients in our study were treated with first line 2nd generation TKIs which have been demonstrated to induce earlier and higher rates of CCyR and MMR compared to imatinib [21,22]. This may partially account for the difference in 12-month response rates.

Stopping TKI therapy provides a novel opportunity to obtain TFR for approximately 40% - 60% of patients [8]. The STIM trial was one of the first studies to confirm the possibility of achieving TFR. This study highlighted that most patients who relapsed did so within the first 6 months of treatment discontinuation and that all patients who relapsed remained sensitive to imatinib re-introduction [23]. The safety of imatinib discontinuation was re-affirmed by the TWISTER trial [24]. Moreover, interim analysis of the STOP 2G-TKI study revealed that discontinuation of 2nd generation TKIs yields promising TFR rates in addition to allowing effective re-introduction of TKIs without safety concerns [25]. The safety and stability of response in those who have successfully achieved TFR has been recently reaffirmed by the Australasian Leukaemia & Lymphoma Group (ALLG). The ALLG have previously demonstrated the persistence of BCR-ABL1-positive cells, even in patients with a sustained TFR [26]. They have now revealed that despite an absence of ongoing TKI therapy, there is an ongoing fall in minimal residual disease [27].

The exact pre-conditions for identifying patients suitable for TKI therapy cessation without fear of molecular relapse are currently unknown. However, several studies have begun to address this. The STOP 2G-TKI study identified that a history of TKI treatment resistance was predictive of potential molecular relapse, whereas the EURO-SKI trial highlighted that a longer duration of imatinib therapy was significantly associated with a higher probability of molecular relapse free survival [25,28].

The clinician must recognise the potential problems associated with TKI discontinuation. In addition to disease relapse, the psychological impact of stopping TKI therapy must be considered. An Italian survey revealed that almost 50% of patients had concerns over stopping TKI therapy due to potential disease relapse [29]. Moreover, a relatively new entity to emerge from discontinuation is the TKI withdrawal syndrome, affecting up to 60% of patients and typically manifesting as musculo-skeletal pain. It is often self-limiting but may persist for several months and require treatment with simple analgesia [30].

Little data exists on application of eligibility criteria in a CML population outside clinical trial milieux. Using the 2017 UK Interim Expert Report we identified that 20% of patients could stop TKI therapy, whereas, utilising the EURO-SKI criteria Geelen *et al,* only 11% of patients met the eligibility criteria [15].

There are limitations to our study. This was a population-based study and those involved were not monitored as strictly as during a clinical trial. The International Scale for reporting *BCR-ABL1* results was only recently available to our laboratory, therefore the majority of results were reported using the local assay.

CONCLUSION

In conclusion, our real-world observations show that 1st and 2nd line TKI therapy is effective, however problems with treatment intolerance and failure remain. Additionally, this study identifies a cohort of patients, using the recently published 2017 UK Interim Expert Opinion on Discontinuing TKI Treatment guidelines, who may attempt TKI therapy cessation. Our findings have revealed that criteria for an attempt to stop TKI therapy are met by one fifth of patients.

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