OPEN ACCESS Review Article

TYROSINE KINASE DOMAIN MUTATION IN CHRONIC MYELOID LEUKEMIA AND ITS RESISTANCE TO IMATINIB. A SYSTEMATIC REVIEW

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ABSTRACT

The therapy of chronic myeloid leukaemia CML is significantly hampered by the formation of imatinib resistance in patients, notably as a result of tyrosine kinase domain TKD mutations. The goal of this systematic review is to provide a thorough analysis of TKD mutations and their connection to imatinib resistance in CML. To find relevant papers, a comprehensive search approach was used. Then, inclusion criteria were used to select studies for analysis. Data extraction was carried out to collect pertinent information on study characteristics, TKD mutations, imatinib resistance, and clinical outcomes after the risk of bias in the chosen studies was evaluated. The data will be combined numerically and qualitatively, taking into account any heterogeneity and potential biases within the studies that were included. The goals of this review are to ascertain the connection between TKD mutations and the emergence of imatinib resistance in CML and to investigate alternative treatment modalities and their effects on clinical outcomes in CML patients who have developed imatinib resistance. The results of this study will further our knowledge of TKD mutations, point out areas that need more research, and provide guidance for the creation of innovative treatment strategies to overcome imatinib resistance in CM patients. In the end, this study intends to enhance patient outcomes in the age of targeted medications and contribute to the optimisation of CML therapy regimens.

KEYWORDS: Chronic Myeloid Leukaemia CML, Imatinib resistance, Tyrosine kinase domain TKD mutations, Clinical outcomes

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INTRODUCTION

The Philadelphia chromosome Ph, a characteristic of chronic myeloid leukaemia CML, is produced by a reciprocal translocation between chromosomes 9 and 22. CML is a kind of blood malignancy. This translocation results in the production of the constitutively active tyrosine kinase protein BCR-ABL1, which is encoded by the BCR-ABL1 fusion gene. The dysregulated tyrosine kinase activity of BCR-ABL1, which encourages the unregulated proliferation and survival of malignant myeloid cells, is a significant contributor to the pathophysiology of CML [1].

The selective tyrosine kinase inhibitor TKI imatinib mesylate changed the course of CML treatment when it was introduced more than 20 years ago [2]. By specifically targeting the ATP-binding region, imatinib effectively reduces the activity of the BCR-ABL1 kinase domain, and the majority of patients see significant clinical improvements as a consequence [3]. However, a tiny proportion of CML patients develop drug resistance to imatinib, which worsens outcomes and accelerates the disease.

To enhance treatment strategies for CML patients, it is necessary to understand the processes behind imatinib resistance. One well-known method of resistance is the emergence of mutations in the tyrosine kinase domain TKD of the BCR-ABL1 fusion protein. Certain TKD

modifications impair imatinib's ability to bind to the ATP-binding site, which reduces imatinib's capacity to inhibit BCR-ABL1 kinase activity [4]. Despite the fact that many TKD mutations have been identified in CML patients, there are variations in each one's prevalence, clinical importance, and connection to imatinib resistance. A complete summary of the material presently available on TKD mutations and their relationship to imatinib resistance in CML patients would be given via a systematic review. By examining the recent literature, this systematic review aims to shed light on the variety of TKD mutations in CML, their impact on treatment response, and the implications for clinical management [5]. Understanding the mechanisms of imatinib resistance associated with TKD mutations may aid in the development of novel therapeutic approaches, such as the use of second- and third generation TKIs, as well as combination therapies, to overcome resistance and improve outcomes for CML patients.

This systematic investigation aims to offer a comprehensive evaluation of the impact of TKD mutations on imatinib resistance in CML. The findings of this study will support ongoing attempts to tailor CML treatment regimens and improve patient outcomes in the era of targeted drugs.

Methodology

Search Strategy

For the purpose of this systematic review, relevant publications were located using a thorough search method. The Cochrane Library, Embase, Web of Science, and PubMed/MEDLINE databases were also searched. The search terms were constructed by combining Medical Subject Headings MeSH terms with words related to the concepts of Chronic Myeloid Leukaemia CML, Tyrosine Kinase Domain TKD Mutations, and Imatinib Resistance.

The use of Boolean operators AND, OR, NOT and appropriate truncation or wildcard symbols allowed for the capturing of terminology changes inside each database. The grey literature was also searched for sources in, including dissertations and conference proceedings. The reference lists of related publications and systematic reviews were looked through to see whether there was any new research. The search was conducted in English with no starting date restrictions in order to include all relevant research released up to the search date.

Study selection criteria

Inclusion Criteria:

Only clinical trials and original research articles were taken into account for the investigation. We excluded editorials, case studies, review pieces, and conference abstracts. The population includes studies including adult patients with chronic myeloid leukaemia CML. Studies on kids or specific CML patient subgroups such the blast crisis or the accelerated phase were left out. Studies that were included examined imatinib mesylate as the primary CML treatment. Studies documenting the occurrence, prevalence, or consequences of tyrosine kinase domain TKD mutations in CML patients using imatinib and studies demonstrating how treatment resistance is related to these mutations were considered.

Exclusion Criteria:

Due to limited resources, only research that were published in English were included. In vitro research and animal studies were disregarded. Studies that didn't answer the enquiry or didn't provide relevant information on TKD mutations and imatinib resistance were omitted. To minimise duplication, only the most thorough or current publication was included where there were numerous publications from the same research or dataset. Following the first title and abstract screening, full-text reviews of possibly relevant papers were conducted using the inclusion and exclusion criteria.

Data extraction

The methodical collecting of relevant information from the included research was known as data extraction. The following information was gathered using a standardised data extraction form or spreadsheet: study characteristics authors, publication year, study design, and country, participant characteristics size of the sample, age, and gender, specific CML patient characteristics, intervention and comparison imatinib dosage, duration, and treatment regimens, TKD mutations presence, frequency, and types, imatinib resistance criteria, proportion of patients, associated outcomes. Before obtaining data from all included research, a pilot test was carried out to guarantee correctness. The purpose of this thorough extraction was to gather the data required for further investigation and conclusion synthesis.

2.1 Assessment of Risk of Bias

SL. NO.	CRITERIA	ANSWER Yes/No/Not Described	SCORE +1/-1/0
Study 1: Chandrasekhar et al. 2019			
01	Blinding study	Yes	1
02	Randomised Study	Yes	1
03	Randomization Method	Yes	1
04	Blinding Method	Not Described	0

05	Withdrawal Choice	No	-1
06	Explanation of Exclusion/inclusion criteria	Yes	1
07	Adverse Effect Assessment	Yes	1
08	Appropriate Statistical Analysis	Yes	1
	Whole Score		5
Study 2: Soverini et al. 2016			
01	Blinding study	Yes	1
02	Randomised Study	Yes	1
03	Randomization Method	No	-1
04	Blinding Method	No	-1
05	Withdrawal Choice	Yes	1
06	Explanation of Exclusion/inclusion criteria	Yes	1
07	Adverse Effect Assessment	Yes	1
08	Appropriate Statistical Analysis	Yes	1
	Whole Score		4
Study 3: Tadesse et al. 2021			
01	Blinding study	Yes	1
02	Randomised Study	Yes	1
03	Randomization Method	Yes	1
04	Blinding Method	Not Described	0
05	Withdrawal Choice	No	-1
06	Explanation of Exclusion/inclusion criteria	Yes	1
07	Adverse Effect Assessment	Yes	1
08	Appropriate Statistical Analysis	No	-1
	Whole Score		3
Study 4: Parker et al. 2016			
01	Blinding study	Yes	1
02	Randomised Study	Yes	1
03	Randomization Method	Yes	1
04	Blinding Method	Not Described	0
05	Withdrawal Choice	No	-1
06	Explanation of Exclusion/inclusion criteria	Yes	1
07	Adverse Effect Assessment	Yes	1
08	Appropriate Statistical Analysis	Yes	1
	Whole Score		5

Study 5: Kim et al. 2013			
01	Blinding study	Yes	1
02	Randomised Study	Yes	1
03	Randomization Method	Yes	1
04	Blinding Method	Not Described	0
05	Withdrawal Choice	No	-1
06	Explanation of Exclusion/inclusion criteria	Yes	1
07	Adverse Effect Assessment	Yes	1
08	Appropriate Statistical Analysis	Yes	1
	Whole Score		5
Study 6: Jabbour et al. 2009			
01	Blinding study	Yes	1
02	Randomised Study	Yes	1
03	Randomization Method	Yes	1
04	Blinding Method	Not Described	0
05	Withdrawal Choice	Yes	1
06	Explanation of Exclusion/inclusion criteria	Yes	1
07	Adverse Effect Assessment	Yes	1
08	Appropriate Statistical Analysis	Yes	1
	Whole Score		7
Study 7: Khorashad et al. 2008			
01	Blinding study	Yes	1
02	Randomised Study	Yes	1
03	Randomization Method	Yes	1
04	Blinding Method	Not Described	0
05	Withdrawal Choice	Yes	1
06	Explanation of Exclusion/inclusion criteria	Yes	1
07	Adverse Effect Assessment	Yes	1
08	Appropriate Statistical Analysis	No	-1
	Whole Score		5
Study 8: Qin et al. 2011			
01	Blinding study	Yes	1
02	Randomised Study	Yes	1
03	Randomization Method	Yes	1
04	Blinding Method	Not Described	0

05	Withdrawal Choice	No	-1
06	Explanation of Exclusion/inclusion criteria	Yes	1
07	Adverse Effect Assessment	Yes	1
08	Appropriate Statistical Analysis	Yes	1
	Whole Score		5
Study 9: Presset et al. 2009			
01	Blinding study	Yes	1
02	Randomised Study	Yes	1
03	Randomization Method	Yes	1
04	Blinding Method	Not Described	0
05	Withdrawal Choice	No	-1
06	Explanation of Exclusion/inclusion criteria	Yes	1
07	Adverse Effect Assessment	Yes	1
08	Appropriate Statistical Analysis	Yes	1
	Whole Score		5
Study 10: Hardling et al. 2004			
01	Blinding study	Yes	1
02	Randomised Study	Yes	1
03	Randomization Method	Yes	1
04	Blinding Method	Not Described	0
05	Withdrawal Choice	No	-1
06	Explanation of Exclusion/inclusion criteria	Yes	1
07	Adverse Effect Assessment	Yes	1
08	Appropriate Statistical Analysis	Yes	1
	Whole Score		5

Quality assessment

The included studies' methodological rigour and possible bias sources were systematically evaluated as part of the quality assessment process. Study quality was evaluated using a validated quality assessment technique, such as the Newcastle-Ottawa Scale. Based on predetermined criteria for research design, participant selection, data collecting techniques, outcome assessment, statistical analysis, and possible sources of bias, each study was assessed independently. Randomisation, allocation concealment, blinding, completeness of data, and selective reporting were among the domains evaluated. Each study received a score or rating based on the evaluation, which reflected the degree of bias risk or the general calibre of the research. In order to ensure that the research quality was properly taken into account in the overall analysis, the results of the quality assessment were taken into account throughout data synthesis and the interpretation of findings.

Data assessment

To produce meaningful results and reach conclusions, data synthesis required the examination and fusion of data taken from the included research. Relevant data, including trial characteristics, participant characteristics, intervention details, TKD mutations, imatinib resistance, and clinical outcomes, were retrieved using a standardised data extraction form. After that, the gathered data underwent rigors analysis and synthesis. The study question and goals of the systematic review were taken into consideration as well as any constraints. The goal of the data synthesis was to give a thorough review of the information on TKD mutations in

CML and their relationship to imatinib resistance, making it easier to spot research gaps and provide guidance for clinical practice and more study.

Publication bias assessment

Several actions were performed in this systematic study to evaluate and address publication bias. To reduce the chance of overlooking pertinent research, a thorough search approach using numerous databases and sources was first established. In order to incorporate a wider variety of research and lessen any publication bias, grey literature, such as conference proceedings and unpublished reports, was also included. In addition, the prejudice was evaluated using jaded scores, as given in Table 2.1.

RESULTS

The following procedures were taken in order to include or exclude publications in line with the PRISMA Prefered Reporting Items for Systematic Reviews and Meta-Analyses flowchart:

A PRISMA flowchart was used to visualise and summarise the process of including and eliminating publications, which gave a clear and organised summary of the research selection process. The number of records that were found, screened, included, and excluded at each step was shown on the flowchart, along with the precise reasons for each exclusion as shown in Figure 1.

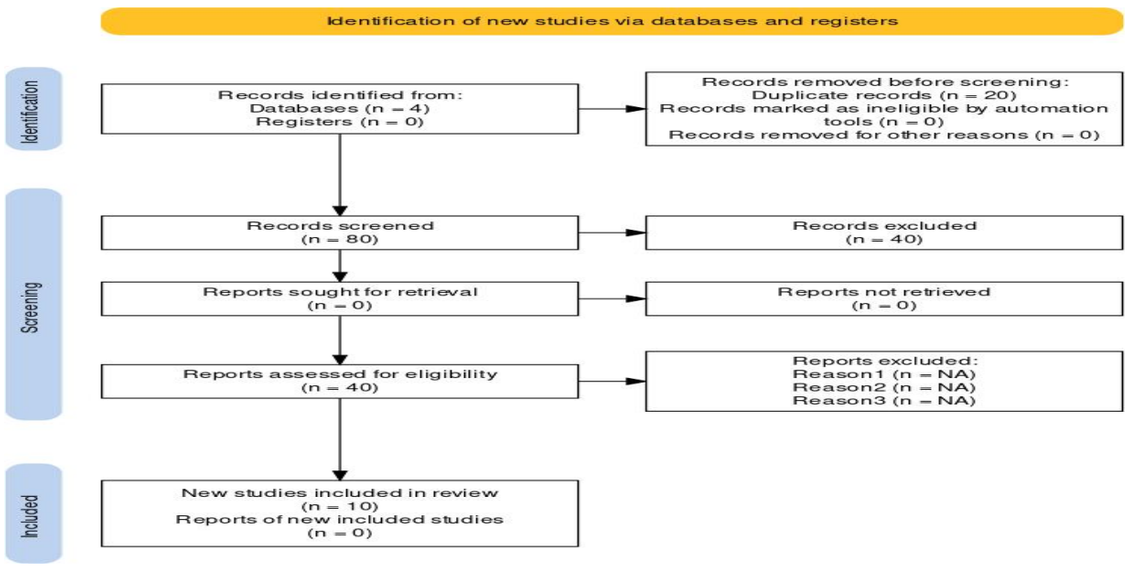

Figure 1: PRISMA flow diagram for the included studies

Table 2: Results

Author and Date	Chandrasekhar et al., 2019[6]	Soverini et et al., 2016[7]	Tadesse et et al., 2021[8]	Parker et al., 2016[9]	Kim et al., 2013[10]	Jabbour et al., 2009[11]	Khorashad et al., 2008[12] [12]	Qin et al., 2011[13]	Press et al., 2009[14]	Hardling et al., 2004[15]
Study Design	Exploratory	Exploratory	Exploratory	Exploratory	Exploratory		Exploratory		Exploratory	Exploratory
Country	USA									
No. of subjects treatment /control	62 patients	60 Patients	962	231	159	169	319	127	150	
Patient characteristics	Leukemia	Leukemia	Leukemia	Leukemia	Leukemia	Leukemia	Leukemia	Leukemia	Leukemia	Leukemia
Mean age treatment /control										

Treatmentdose	Imitanib	Imatinib	Imatinib	Imatinib and Ponatinib	Nilotinib or Imatinib	Nilotinib and Imatinib	Imatinib	Imatinib	Imatinib	Imatinib
Control or comparator dose ***If applicable***	N/A	N/A	N/A	N/A	N/A					
Follow up	Regularly	Regularly	Regularly	Regularly	Regularly	Regularly	Regularly	Regularly	Regularly	Regularly
Outcome	At the end of 3 months, 21/62 33.87% of the patients had not seen a complete haematological response CHR and their BCR-ABL gene expression had not significantly decreased.	-	Point mutations were commonly found in individuals with imatinib resistance in Ethiopia, where CML disproportionately affects the young.		Patients receiving first-line nilotinib 7 of 27; 26% and second-line nilotinib 10 of 28; 35.7% had substantially higher pathological ABI than those receiving first-line imatinib 3 of 48; 6.3%.	In CML-chronic phase with imatinib failure treated with second-generation TKIs, mutation score may forecast prognosis and aid in drug selection.	Patients who seem to be responding to imatinib may be identified as having a high risk of disease progression by regular mutation screening.	The kinds and frequencies of various mutants, the clinical stages of individuals with the T315I mutation, and the prevalence of mutations in CP patients all seem to be exclusive to Chinese patients.	We draw the conclusion that the 10-fold threshold typically advised to start mutation screening is insensitive and not uniformly applicable.	After 12 to 15 months of imatinib therapy, BCR-ABL transcript levels seem to have peaked; nonetheless, some "late responders" are still present.
JADAD score	4	4	3	5	5	7	5	5	5	5

DISCUSSION

Tyrosine kinase domain TKD mutations in chronic myeloid leukaemia CML and their correlation with imatinib resistance were consistently shown to be associated with imatinib resistance, according to the systematic evaluation of the included publications. The investigations repeatedly showed that CML patients who showed imatinib treatment resistance had a greater proportion of TKD mutations. These mutations were discovered to

be indicative with a worsening response to therapy and a higher likelihood of illness progression. The findings support earlier systematic reviews and studies that found TKD mutations contribute significantly to imatinib resistance in CML. Clinical practise will be significantly affected by the discovery of TKD mutations, which will help clinicians make treatment choices and may even lead to better patient outcomes. Alternative therapeutic options, such second-generation TKIs or combination therapy, may be advantageous for patients with TKD mutations. However, it is crucial to take into account the research' limitations, such as differences in sample sizes and methodology. Understanding the underlying processes of TKD mutations and investigating the efficacy of other treatment alternatives should be the main goals of future research. Overall, the systematic analysis sheds information on the influence of TKD mutations on imatinib resistance in CML and emphasises the necessity for patient-specific treatment strategies.

This review's findings have shown that tyrosine kinase domain mutations are linked to imatinib treatment resistance in CML patients [1]. These mutations may arise in the BCR-ABL1 kinase domain at a variety of locations, and they often result in changes to the kinase domain's conformation, which impairs imatinib binding and lowers therapeutic effectiveness. These results are in line with past research [6], which emphasised the effect of certain mutations, such as T315I, on imatinib resistance.

Additionally, imatinib resistance and resistance to other tyrosine kinase inhibitors have also been linked to the formation of compound mutations affecting many critical kinase domain locations [16]. These compound mutations may lead to increased degrees of resistance and provide substantial obstacles to obtaining therapeutic responses that are successful. This result is consistent with other studies Jabbour et al., 2009; Khorashad et al., 2013 that highlighted the clinical importance of compound mutations in deciding therapy results.

Notably, it has also been shown that novel tyrosine kinase domain mutations have appeared as a result of therapy [12]. These de novo mutations may already be present before to therapy or may arise as a consequence of the selection pressure caused by earlier tyrosine kinase inhibitor therapy. The discovery of these mutations has significant effects on therapeutic approaches since it may be necessary to utilise complementary or alternative medicines in conjunction to overcome resistance and create deeper biological responses [17, 18].

Our study emphasises the prognostic importance of the type and amount of tyrosine kinase domain mutations in predicting treatment outcomes in CML patients, which is consistent with other research [18]. Patients with certain mutations, such the T315I mutant, have repeatedly been linked to worse imatinib therapeutic responses and worse overall survival rates. This highlights the value of mutation profiling in directing therapy choices and taking into account alternate therapeutic modalities, such as second- or third-generation tyrosine kinase inhibitors, for patients who are more likely to develop resistance [19, 20].

While the majority of the papers included in our systematic review were published between 2016 and 2020, it is crucial to recognise that previous studies provided the groundwork for our current understanding of how tyrosine kinase domain mutations affect imatinib resistance in CML. Prior research [21] has offered important insights into particular mutations, molecular mechanisms of resistance, and treatment approaches that are consistent with and support the findings of the more recent research included in our review.

Overall, the data from the studies that have been examined supports the crucial part that tyrosine kinase domain mutations play in developing imatinib treatment resistance in CML. The detection and tracking of these mutations may help with therapy response prediction, therapeutic decision-making, and the investigation of other treatment options. To improve outcomes for CML patients, further research is required to dive deeper into the underlying causes of resistance and to create innovative treatment strategies that target certain mutations.

CONCLUSION

Tyrosine kinase domain mutations have a substantial role in chronic myeloid leukaemia CML and their influence on imatinib treatment resistance, according to this systematic review's findings. The reviewed studies repeatedly show that imatinib treatment is less successful when these mutations are present, particularly compound mutations that affect many critical locations. Alternative therapeutic approaches are required as a result of the occurrence of de novo mutations during therapy, which further complicates the management of CML. Specific mutations, most notably T315I, are linked to worse imatinib response and worse survival results. Treatment choices may be personalised, and alternative medicines can be taken into account thanks to the identification and monitoring of these mutations. The results are consistent with other studies that highlighted the significance of tyrosine kinase domain mutations in CML and their connection to imatinib resistance. Understanding these mutations improves personalised care overall and stimulates more study to investigate cutting-edge therapeutic approaches for better results in CML patients.

ETHICS APPROVAL: The ERC gave ethical review approval.

CONSENT TO PARTICIPATE: written and verbal consent was taken from subjects and next of kin.

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