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Review Article

Treatment of T315I mutation: Indian perspective

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ABSTRACT

The management of chronic myeloid leukemia (CML) has evolved significantly with the introduction of tyrosine kinase inhibitors. However, the emergence of resistance, particularly the T315I mutation, poses a formidable challenge. This review examines current treatment options for T315I mutation, focusing on their efficacy and availability, with a specific emphasis on the Indian perspective. While drugs such as ponatinib, omacetaxine mepesuccinate, asciminib, and PF-114 have shown promise against T315I mutation, their limited availability and high cost present significant barriers in the Indian context. Moreover, poor tolerability and adverse effects with existing treatments further complicate the treatment landscape. Efforts to improve access to novel therapies and explore alternative treatment modalities are essential to address this challenge and improve outcomes for patients with T315I-mutant CML and philadelphia-positive acute lymphoblastic leukemia.

Keywords: T315I mutation, Ponatinib, Asciminib, Interferon-alpha, Allogenic stem cell transplant

INTRODUCTION

The journey of chronic myeloid leukemia (CML) has been full of hurdles and success stories. T315I is the latest hurdle being faced in this tyrosine kinase inhibitor (TKI) era. The first probable case reported ever was in 1842 by Donne in Paris, which was followed 3 years later by two publications, after which the term "Leukemia" was recognized.[1] Almost after 115 years, the Philadelphia chromosome was recognized.[2] For 100 years after the recognition of CML, there was no treatment available, and it was a dreaded disease with 100% mortality. After World War 2, nitrogen mustard was found to reduce the leukocyte count; however, it did not contribute much to survival. Following this, busulphan, hydroxycarbamide, allogenic stem cell transplant, and interferon-alpha (IFN-α) were used for the treatment of CML. These treatment modalities also did not benefit patients. Then came the path-breaking discovery of TKI "Imatinib Mesylate", which got approval in 2001. This revolutionized the treatment of CML, making it, in literal meaning, a "chronic" disease. The 8-year survival rate increased from 6% to 87% with the use of imatinib.[3] After its discovery, 2nd and 3rd-generation TKIs were also discovered, catering to the need to treat point mutations in the tyrosine kinase domain (KD), which resulted in imatinib resistance. Imatinib resistance is also a problem in treating Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL).

IMATINIB RESISTANCE: MECHANISM

Resistance to imatinib has been categorized as breakpoint cluster region–Abelson (BCR-ABL) dependent or independent. Most commonly, the KD mutations are the cause of acquired

resistance. These KD mutations are further categorized into 4 types based on the regions involved. These are the ATP-binding loop (P-loop), such as E255K and Y253F/H and the activation loop (A-loop), such as H396R, the drug binding site, and the catalytic site.[4] The most common mutation is P-loop mutation, which causes 70–100-fold more resistance to imatinib. However, second-generation TKIs do have an activity against these mutations. The key challenge in the treatment of imatinib-resistant CML is another frequently occurring mutation, T315I, also known as the "gatekeeper" mutation. T315I holds a special place as neither imatinib nor the 2nd-generation TKIs act against this mutation. It completely impairs the contact between the ABL tyrosine KD and TKI, resulting in a high maximum 50% inhibitory concentration to these TKIs.[5] Hence, the new research is directed toward overcoming this resistance.

TREATMENT OPTIONS AVAILABLE FOR T315I MUTATION

Treatment options available for T315I mutation are limited. These include 3rd-generation TKI ponatinib and olverembatinib, protein synthesis inhibitor omacetaxine mepesuccinate, allogenic stem cell transplant (allo-SCT), specifically targeting the ABL myristoyl pocket inhibitor asciminib, and the very recent, 4th-generation TKI, PF-114. Ponatinib, a pan-tyrosine kinase inhibitor, has shown efficacy and safety along with a durable 5-year follow-up response in phase 2, PACE trial.[6] Olverembatinib, another 3rd-generation TKI active against T315I mutation, is approved only in China at present.[7] Omacetaxine mepesuccinate subcutaneous injection has shown activity against T315I mutation.[8] However, due to its limited availability in countries other than the United States, it is not widely used. Allo-SCT is now an age-old treatment for T315I mutation, but due to the availability of newer drugs active against T315I mutation, it is now considered only in patients in blast crisis or in patients for whom other treatment options are not available. The first-in-class allosteric inhibitor asciminib, which specifically targets myristoyl pocket inducing an inactive conformation of tyrosine kinase, hence exhibiting a unique mechanism of action, has been approved by the Food and Drug Administration against T315I mutation.[9] Myristoyl pockets are present in only a few of the kinases, providing the potential for more selectivity.[10] Moreover, the newest of all, PF-114, inhibits T315I-mutant BCR-ABL at nanomolar concentrations, giving clinical outcomes the same as that of ponatinib. As compared to ponatinib, which has off-target effects leading to cardiovascular complications, PF-114 is more selective in its action, improving its safety profile.[11] However, the availability of these drugs is an issue, making the treatment of T315I-mutant CML or Ph+ ALL difficult.

INDIAN PERSPECTIVE: THE NEWER AND THE OLDER DRUGS

Data from Indian publications show that the T315I mutation is one of the most common mutations found in CML and Ph+ALL patients from India.[12] There is still a crucial gap in the range of drugs available to overcome this resistance.[13] Ponatinib is not widely available in India. Moreover, Indian experience with ponatinib suggests that Indians have poor tolerability to the drug even at the lower doses of 15 mg OD. In 21 patients who received ponatinib across 3 centers in India, 45% of patients had grade 3 or 4 cytopenias, and 20% of patients experienced cardiovascular adverse effects that needed termination of therapy.[14] Omacetaxine mepesuccinate is not available in India. Asciminib has recently been made available by Novartis in India. Asciminib dose for CML-chronic phase (CP) as 3rd-line therapy is 40 mg twice a day, while for T315I mutation, the dose is 200 mg twice a day, which means that the cost of treating T315I mutation with asciminib is 5 times more than that of its usual dose making it out of reach for most patients in India. PF-114 is also not currently available in India and hence excludes it from the available treatment options. Allo-SCT is still an available option for Indian patients. However, the cost of treatment and the morbidity associated with it make it less feasible for patients in CML-CP with T315I mutation. This highlights the unmet need for treating CML-CP patients harboring T315I mutation in India. It is important to revisit the older treatment modalities to see if they are effective against this mutation. IFN-α, which was used in the pre-TKI era, has been tried in this scenario with promising results. Polivkova *et al*. showed a molecular response in 4/6 patients with the mutation, treating them with IFN-α as a single agent or in combination with TKI. Based on the immune profiling, they proposed that the main mechanism leading to the success of the treatment was the immune activation induced with TKI pre-treatment followed by restoration of immunological surveillance with IFN-α therapy.[15] IFN-α, in combination with imatinib 400 mg, has shown responses in T315I mutation, as suggested by case reports. Similarly, Peg-IFN-α has also shown results against this mutation.[16] Hydroxyurea, which has been used for cytoreduction in CML for decades, has also shown activity by inhibiting the proliferation of cells harboring T315I mutation.[17] All these older therapies seem to be promising in treating T315I mutation till the newer therapies become widely available and affordable for Indian patients.

CONCLUSION

Addressing the challenges of treating CML with the T315I mutation in India requires overcoming barriers to access effective therapies. While newer treatments such as ponatinib and asciminib show promise, their limited availability and

high costs hinder patient access. In addition, concerns about tolerability with existing options highlight the need for alternative treatments.

Exploring older therapies such as IFN-α and hydroxyurea present a promising interim solution until newer treatments become more accessible. However, collaborative efforts among healthcare stakeholders are crucial to bridge the gap in treating T315I-mutant CML effectively in India. By improving access to innovative therapies and re-evaluating older treatment modalities, we can enhance outcomes for patients facing this challenging mutation.

Ethical approval

Institutional Review Board approval is not required.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that they have used artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript or image creations.

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