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Response of Second Generation Tyrosine Kinase Inhibitors in the Patients with CML at a Tertiary Care Hospital in the North Western India.

1. **Dr. Sudhir Attri (Professor and Head, Department of Medicine, PGIMS Rohtak)**
2. **Dr. Vikas Bhatthi (Associate Professor, Department of Medicine, PGIMS Rohtak)**
3. **Dr. Dushyant Sharma (Research Consultant at PGIMS Rohtak, email id dushyantsharma37500@gmail.com)**
4. **Dr. Avani Sharma (MBBS Intern, PGIMS Rohtak)**
5. **Dr. Srishti (MBBS Intern, PGIMS Rohtak)**

CORRESPONDING AUTHOR:Dr. Dushyant Sharma (Research Consultant at PGIMS Rohtak, email id dushyantsharma37500@gmail.com)

Abstract:

Introduction: Chronic myeloid leukemia is characterized by the dysregulated growth of granulocytes, driven by the Philadelphia chromosome translocation. The prevalence of CML is higher in men, with a median age of 57 years and a five-year survival rate of 85%. Tyrosine kinase inhibitors such as Imatinib have revolutionized CML treatment. However, resistance or intolerance to first-line Imatinib requires second-generation TKIs like Nilotinib and Dasatinib. This study aims to evaluate the response of patients treated with these TKIs at a hematology clinic. **Methods:** This retrospective study analyzed 100 randomly selected CML patients treated between 2020 and 2022. Data were collected on patient demographics, disease progression, treatment regimens, and response rates. Patients who started on Imatinib and later switched to second-line TKIs due to resistance or side effects were followed to assess treatment efficacy. **Results:** The cohort had a median age of 43 years, with 52% males and 48% females. Most patients (95%) initiated treatment with Imatinib, with 6% experiencing mild side effects and 4% severe side effects leading to treatment changes. In patients resistant to Imatinib, second-generation TKIs showed favorable responses: Dasatinib was effective in patients with advanced disease, while Nilotinib was useful for those intolerant to Imatinib. One patient resistant to both was successfully treated with Bosutinib, a third-generation TKI. **Conclusion:** Our findings highlight the efficacy of second-generation TKIs for managing Imatinib-resistant CML. Dasatinib and Nilotinib effectively managed disease progression, though side effects were a concern. The use of third-generation TKIs like Bosutinib provides additional therapeutic options for refractory cases.

Keywords: Chronic myeloid leukemia (CML); Imatinib; Nilotinib; Dasatinib; Bosutinib

Introduction:

Chronic myeloid leukemia is a condition characterized by dysregulated generation and uncontrolled growth of fully developed and developing granulocytes. The prevalence of this

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condition is higher among those in the older age group, with a median age of 57 years, and the five-year survival rate is around 85%. The prevalence of this condition is higher in men by comparison to females. In addition to the characteristic Philadelphia chromosomal translocation, exposure to ionizing radiations is a significant contributing factor.[1]

Approximately one hundred percent of patients have a balanced reciprocal translocation between the long arm of chromosome 9 and 22 due to BCR-ABL Translocation. Most instances, over 95%, exhibit foreshortening of the long arm of Chromosome 22 (Philadelphia Chromosome), resulting in a positive constitutive ABL Kinase Activity.[2]

The illness may manifest in three stages. In 85% of instances, it has a chronic course and, if left untreated, it advances to an accelerated and blastic phase within four years, resulting in a grim prognosis.[3]

Most often, patients may have asymptomatic neutrophilia. Symptomatic individuals may exhibit tiredness, splenomegaly, and often hyperviscosity and symptoms associated to Leucostasis. The diagnosis may be established by analyzing the blood picture, results from the bone marrow, FISH, and identifying BCR-ABL transcripts using DNA PCR. It is more likely for people with Chronic Myeloid Leukaemia to develop tumour lysis syndrome compared to other myeloproliferative disorders for which they receive treatment. 300mg of Allopurinol taken orally.[4]

Tyrosine kinase inhibitors have emerged as the primary treatment method for chronic myeloid leukemia (CML) in recent years. Imatinib is the predominant tyrosine kinase inhibitor (TKI) used as standard first-line treatment. It is used in conjunction with hydroxyurea to reduce the numbers. Clinical trials have shown a positive response to Imatinib treatment. However, individuals with BCR-ABL domain mutations exhibit inadequate or even poor response to imatinib. Under such circumstances, patients should be prescribed second-generation tyrosine kinase inhibitors (TKIs) such as Nilotinib and Dasatinib. In many instances, there may exist a T315 1 mutation that is resistant to second-line medications and should be treated with third-generation TKIs such as Ponatinib. The last option for therapy is the implantation of allogenic haematopoietic stem cells.[5]

Following Imatinib's long-standing use as the primary treatment for chronic myeloid leukaemia for more than 10 years, two more medicines have shown greater potency than imatinib and enhanced effectiveness in treating chronic CML, particularly in patients with Imatinib resistant BCR-ABL Domain mutations.[6]

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 09, 2024

Multiple studies have shown that inadequate compliance with imatinib has adverse consequences on the patients' reactions. Therefore, patients who have not achieved the required response with imatinib should be evaluated for second-line medications such as Nilotinib.[7–9]

An investigation conducted among patients in Karbala district of Iraq revealed that over 66% of patients had obtained significant molecular response after initiating the new treatment with a second-line medication (Nilotinib). The therapeutic intervention achieved a significant decrease in the BCR-ABL transcription level without any adverse effects, therefore establishing its safety and efficacy as a second-line therapy for Iraqi patients.[10,11]

Furthermore, Dasatinib has shown superiority over Imatinib in individuals with recently diagnosed chronic phase CML. Nevertheless, second line medications bring along their own set of adverse consequences. Although Dasatinib is more associated with pleural effusion. Treatment with Nilotinib has been associated with dermatological toxicity in individuals.[12,13] The objective of this research is to examine the response of individuals using different tyrosine kinase inhibitors for the treatment of CML at our Centre's Hematoncology clinic, which offers both first line and second line therapy modality.

Methods

The study was conducted retrospectively, focusing on a comprehensive analysis of data obtained from patient records and treatment charts of individuals who sought treatment for chronic myeloid leukemia (CML) at our institution during the years 2020, 2021, and 2022. The use of a retrospective design enabled us to assess patient outcomes by analyzing past data, therefore offering significant insights on the effectiveness of therapy, patterns of response, and overall care of CML over that period.

The main aim of the research was to determine the first therapeutic methodologies used in CML patients at the beginning of their therapy. This includes assessing whether patients received first-line regimens such as tyrosine kinase inhibitors (TKIs) or other therapy approaches. Moreover, the research sought to evaluate the patients' reactions to these treatments on a long-term basis, pinpointing significant events such as full cytogenetic response (CCyR), major molecular response (MMR), or other signs of successful treatment. Aside from evaluating response rates, we also analyzed the progression of treatment plans during therapy, including modifications in medication, dose optimizations, or the implementation of second-line treatments as needed.

The data collection and analysis took place in the hematology clinic, which is located within the cancer ward of our institutional facility. This clinic functions as a specialised facility for the treatment and control of hematological malignancies, namely chronic myeloid leukaemia (CML).

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 09, 2024

In order to get a sample that accurately represents the population, we randomly chose 100 patients from the pool of individuals who had used medical services at the clinic throughout the designated three-year timeframe. The objective of the random selection procedure was to reduce selection bias and provide a more comprehensive view of the treatment results across different demographic and clinical characteristics.

The collection of patient sample included persons from various age cohorts, genders, and stages of illness. The incorporation of varied patient profiles for a more thorough examination of how many elements, such as age, disease advancement, and other medical conditions, could have impacted the reactions and results of drug therapy. Furthermore, comprehensive data was obtained from patient records pertaining to the length of therapy, encountered side effects, compliance with recommended medicines, and any problems or adverse events that may have occurred during treatment.

Adopting this technique enabled us to get a detailed comprehension of the treatment environment for chronic myeloid leukaemia at our institution, therefore facilitating the identification of patterns in therapeutic efficacy and the possible need for alternative strategies. The results obtained from this retrospective study will provide a valuable contribution towards the enhancement of patient care, the optimization of treatment approaches, and the general improvement of future management of chronic myeloid leukemia.

Results:

The research included a random sample of one hundred patients, with women accounting for 48% and men for 52%. Approximately 27% of the patients fell between the age range of 50 to 70 years, with a median age of 43 years. The total median age observed was 57 years. Approximately 47% of the patients are between the age range of 30 to 40 years. A total of 19% of patients arrived to the clinic during the Chronic Phase of the disease, whereas 4% had a blast crisis. 61% of patients were incidentally identified with chronic myeloid leukaemia after exhibiting asymptomatic neutrophilia in the blood picture, whereas 6% were in the accelerated phase. The majority of patients had anemia upon diagnosis, but a few additionally showed mild to severe splenomegaly at their first hospital visit. Each patient underwent molecular typing and DNA-PCR for the BCR-ABL gene transcript. All patients had a Philadelphia chromosome t (9;22) major Transcript, but none of them had a deletion of 20q, trisomy 8, deletion 3q, or double Philadelphia chromosome. Approximately 95% of these patients were started on Imatinib treatment at a dosage of 400mg once daily. Among them, 6% had mild side-effects such as abdominal discomfort, urticaria, fever, generalised weakness, and weariness. A small proportion of patients, specifically 4%, had severe

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 09, 2024

side effects such as bone marrow depression and Pancytopenia. In such cases, Imatinib was temporarily halted and either restarted or the patients were switched to a different medication. All patients were given Folate 500 mg tablets as a supplement.

A single patient had perceptible purpura while on Imatinib, while another patient had a drug reaction to Imatinib, Allopurinol, and hydroxyl urea. However, the chronic myeloid leukemia (CML) was well managed. The patient was first prescribed Nilotinib 300mg twice day and then switched back to Imatinib.

The symptoms subsided. In another patient diagnosed with Leucocytoclastic Vasculitis, treatment was temporarily halted. When the patient resumed treatment, he experienced a blast crisis. To address this, he was prescribed Dasatinib 70 mg twice daily. Over a period of 3 weeks, he became asymptomatic and has been responding well without any adverse effects.

A second patient had an allergic reaction to Imatinib and was subsequently switched to Dasatinib 70mg twice day, demonstrating a positive response.

One symptomatic patient presented with splenomegaly and was promptly started on Dasatinib 70mg twice day. Although her chronic myeloid leukemia (CML) was effectively managed, she sometimes had back pain but had no other symptoms. She achieved asymptomatic status after 7 months of starting the therapy.

One patient with a less than ideal response to Imatinib was transferred to Nilotinib, which elicited a good response. A female patient who was serendipitously diagnosed with CML during her preoperative consultation for a gynaecological procedure was initially prescribed Dasatinib 70mg twice a day. However, she developed a tolerance to the medication and was then switched to Nilotinib 300mg twice a day. Within two months, she experienced a blast crisis, which prompted her to be again switched back to Dasatinib. Fortunately, she responded well to the treatment. Two mostly asymptomatic individuals were started on Nilotinib and Dasatinib and shown a remarkable response to their individual medications.

A documented instance of chronic myeloid leukemia (CML) well managed with Imatinib resulted in a Blast Crisis when it was discovered that the patient developed resistance to both Imatinib and Dasatinib. Initially prescribed Nilotinib 300mg twice a day, the patient had a less than ideal response. However, he was then offered a trial of Bosutinib 500mg once daily, which showed encouraging results. He was then kept on the same medication and eventually became asymptomatic.

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 09, 2024

Discussion:

This study aimed to assess the response of chronic myeloid leukemia (CML) patients to tyrosine kinase inhibitors (TKIs), particularly second-generation drugs Nilotinib and Dasatinib, following suboptimal responses to Imatinib. Our findings provide insight into the demographic patterns, clinical presentations, and treatment outcomes of CML patients at our center, offering key observations about the efficacy of second-line TKIs and the management of treatment failures associated with Imatinib therapy.

Our study aligns with the literature in demonstrating that CML has a slight male predominance, with 52% of the patients being male and 48% female. This is consistent with existing epidemiological data, showing that CML predominantly affects males, although the sex ratio can vary slightly across studies. The median age of patients in our study was 43 years, slightly lower than the global median age of 57 years. This discrepancy may be due to the specific population studied or differences in access to early diagnosis.[14–19]

A significant proportion of patients (61%) were asymptomatic at the time of diagnosis, with neutrophilia being the primary hematologic abnormality. This is characteristic of the chronic phase of CML, where the disease often goes unnoticed until routine blood tests reveal abnormal results. Approximately 19% of patients presented during the chronic phase, and only 4% had progressed to blast crisis by the time of presentation, emphasizing the importance of early detection and intervention to prevent disease progression.[11,15,20]

Our analysis showed that Imatinib therapy was generally well-tolerated, with 95% of patients being started on this first-line treatment. Most patients experienced mild side effects, such as abdominal pain and fatigue, which were manageable and did not require discontinuation of the drug. However, a small number of patients (4%) experienced severe side effects, including bone marrow depression and pancytopenia, necessitating temporary discontinuation or a switch to second-generation TKIs. This finding is in line with previous studies that have reported similar tolerability and side-effect profiles for Imatinib.[21–24]

In patients who showed suboptimal response or intolerance to Imatinib, second-generation TKIs were highly effective. Nilotinib and Dasatinib demonstrated excellent efficacy in controlling CML in patients who either developed resistance to Imatinib or experienced significant side effects. For instance, a patient with leukocytoclastic vasculitis responded well to Dasatinib after failing Imatinib, and another patient with splenomegaly showed remarkable improvement within seven months of starting Dasatinib therapy. These findings are consistent with other studies showing that Dasatinib is particularly effective in patients with advanced or resistant disease.[25–27]

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 09, 2024

Nilotinib was also shown to be effective in patients who could not tolerate Imatinib or had a suboptimal response. One patient, initially started on Dasatinib and then switched to Nilotinib due to drug intolerance, showed an optimal response after the switch. This mirrors the results from other research, which indicates that Nilotinib has superior efficacy in certain cases of Imatinib resistance.[28,29]

However, it is important to note that second-generation TKIs, while effective, are not without their side effects. In our study, a patient who was started on Dasatinib for CML control developed intolerance and was subsequently switched to Nilotinib. Unfortunately, she progressed to blast crisis, highlighting the challenge of managing advanced cases even with more potent drugs. This underscores the need for continuous monitoring and timely interventions when patients show early signs of treatment failure.[30,31]

Interestingly, one patient who grew resistant to both Imatinib and Dasatinib was given a trial of Bosutinib, a third-generation TKI. This patient showed a promising response, reinforcing the importance of having multiple therapeutic options for managing drug resistance. Bosutinib has been shown in clinical trials to be effective in cases where other TKIs fail, and our findings support its use in such cases.[32,33]

Conclusion

Our study confirms that second-generation TKIs, such as Nilotinib and Dasatinib, are effective alternatives for patients who cannot tolerate or have become resistant to Imatinib. However, their use requires careful monitoring for side effects, and early identification of treatment failures is critical to ensuring optimal patient outcomes. The introduction of third-generation TKIs like Bosutinib may offer additional hope for patients with refractory disease, although more research is needed to confirm their long-term efficacy. Our findings contribute to the growing body of evidence supporting individualized treatment approaches for CML patients based on their specific genetic and clinical profiles.

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ISSN: 0975-3583,0976-2833 VOL15, ISSUE 09, 2024

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