Journal of Carcinogenesis
Covering Genesis to Therapeutics

Journal of Carcinogenesis, ISSN: 1477-3163
2025; Vol 24: Issue 8s, https://carcinogenesis.com/

Reasons of treatment switching from first generation to second and third generations of TKIs among CML patients in Iraq -Kurdistan region from 2014-2024

Ravin R. Rasool[1*], Kawa M. Hassan[2], Nawsherwan S. Muhammed[3]

[*1]Candidate of Clinical Hematology at Kurdistan Higher Council of Medical specialties, Erbil- Iraq.

[2]Department of Medicine, College of Medicine – Hawler Medical University, Erbil- Iraq.

[3]Department of Clinical Hematology-Nanakali Hospital, Department of clinical Hematology- Hiwa Hospital, Hematology-Oncology Department- Azadi Teaching Hospital

***Corresponding author:**

Ravin R. Rasool, Email ID: ravoshexani@gmail.com

ABSTRACT

Background: Chronic myeloid leukemia (CML), is one of the myeloproliferative disorders with a characteristic cytogenetic abnormality resulting in the BCR-ABL fusion gene. Imatinib Mesylate is an effective agent for treating patients in all stages of CML. Imatinib directly inhibits the constitutive tyrosine kinase activity. Imatinib binds to BCR-ABL kinase domain by preventing the transfer of a phosphate group to tyrosine on the protein substrate and the subsequent activation of phosphorylated protein.

Materials and Methods: This cross-sectional study included 90 CML patients at the outpatient clinic of a reference hospital in the Kurdistan Region of Iraq, between 2014 and 2024. The questionnaire was divided into two categories: the first part comprised patients' demographic characteristics, which include sex, age, residency, and chronic disease at time of diagnosis (D.M., HTN, hypothyroidism, asthma, and IHD). The second part consisted of duration of exposure to imatinib, clinical adverse effects at the time of switching, blood characteristics, renal function tests (RFT), liver function tests (LFT), quantitative PCR at the time of switching, and the reason for switching.

Results: This study show the outstanding effectiveness of imatinib was highest in 11-20 months which was 41(45.56%), followed by 1-10 months 19(21.11%) and the lowest rates was found in 31-40 months which was 8(8.89%). The most frequent imatinib-related AEs (any grade) occurring in 45% of total patients were Diarrhea 10(11.11%), Myalgia 7(7.78%), Epigastric pain 5(5.56%), Multiple skin lesion 4(4.44%) and Fatigue 2(2.22%). Furthermore, the effect of long term TKI treatment on kidney function and the incidence and prognosis of chronic kidney disease (CKD) in CML patients, 86 (95.56%) has normal renal function tests (RFT) an only 4(4.44%) has increasing urea and creatinine. On the other hand, 83 (92.22%) has normal liver function tests and only 1 (1.11%) has elevated total bilirubin, 1(1.11%) increasing 1fold, 4(4.44%) patients increasing 2folds and 1(1.11%) increasing 3folds.

Conclusion: In this study imatinib showed superior efficacy and a favorable safety profile in patients with newly diagnosed chronic-phase CML. Furthermore, TKI intolerance should not be called failure anymore; it encourages an immediate change of TKI therapy. Failure refers to situations where physicians or patients switched TKIs due to toxicities, believing that reducing the dose would compromise treatment effectiveness.

Keywords: *Chronic myeloid leukemia, effectiveness of imatinib, Clinical Characteristics, tyrosine kinase inhibitor*

How to Cite: Ravin R. Rasool, Kawa M. Hassan, Nawsherwan S. Muhammed, (2025) Reasons of treatment switching from first generation to second and third generations of TKIs among CML patients in Iraq -Kurdistan region from 2014-2024, *Journal of Carcinogenesis*, *Vol.24, No.8s*, 360-368

1. INTRODUCTION

Chronic myeloid leukemia (CML) is a clonal hematopoietic stem cell disorder that accounts for approximately 15% of adult leukemia (1). The incidence of CML varies from 0.4/100,000 to 1.75/100,000 persons per year. Diagnosis is usually suspected from the complete blood count (CBC) and blood smear. Fluorescence in situ hybridization (FISH) for abnormal chromosome t(9;22)(q34;q11.2) and reverse transcriptase quantitative PCR for the BCR-ABL1 fusion gene help in the final diagnosis (2). CML is clinically staged into the chronic phase (CP), accelerated phase (AP), and blast phase (BP). In untreated patients, progression to BP occurs at a median of 3–5 years after initial diagnosis. When a patient is diagnosed

with CML, the first-line treatment is a TKI. In an open-label, multicenter trial with a crossover design for patients treated with the first-generation TKI imatinib, the estimated overall survival rate at 10 years was 83.3%, and the cumulative rate of major cytogenetic response (MCyR) at the end of the trial was 89.0%.

The most-studied mechanisms of imatinib resistance involve point mutations in the ABL1kinase domain and overexpression of BCR-ABL1,5 although research has also implicated BCR-ABL1–independent mechanisms such as upregulation of SRC kinases in some cases of imatinib failure (3). The second-generation TKIs dasatinib, nilotinib, and bosutinib demonstrate enhanced inhibitory potency toward BCR-ABL1 and have shown efficacy in patients who developed BCR-ABL1 kinase domain mutations while receiving imatinib (4-6).

A total of 82.8% of patients had a complete cytogenetic response (CCyR) (7). Despite the excellent results obtained in clinical trials, approximately 40%–45% of patients discontinue imatinib for various reasons, including unsatisfactory therapeutic outcomes in 16% of patients or primary resistance. Dose escalation after failure of imatinib treatment is an important option, though it is likely to be effective only in some subsets of patients(7, 8). However, it is not recommended in the clinic. For such patients, an important salvage treatment strategy is represented by second-generation TKIs including dasatinib, nilotinib, and bosutinib, which allow recovering a CCyR in about 50% of cases (9). When used as a front-line treatment, second-generation TKIs provide a faster achievement of a higher rate of cytogenetic and molecular responses with respect to imatinib (10). Subsequently, second-generation TKIs have been authorized for the first-line treatment of newly diagnosed Philadelphia chromosome–positive (Ph+) adult CP-CML. Some patients experience treatment failure with second-generation TKIs and require a switch to a different TKI. Intolerance and resistance are major causes of treatment failure. Resistance to TKIs can arise from BCR-ABL1-dependent mechanisms, such as mutations in the kinase domain, overexpression, or amplification of BCRABL1, or BCR-ABL1-independent mechanisms (11). The well studied and most common mechanism is point mutation involving the BCR-ABL1 kinase domain (12). The aim of the study is to assess patient's intolerance, adverse effects, disease relapse and/or refractory to first generation TKI(Imatinib).

2. PATIENTS AND METHODS

This is an observational, cross-sectional, and analytical clinical study, with a sample consisting of 90 CML patients at the outpatient clinic of a reference hospitals in Kurdistan Region- Iraq, between 2014 and 2024. Clinical and laboratory data available since the start of hospital follow-up were analyzed from the medical records of these patients. The initial analysis of the data included all patients who signed a fully informed written agreement to undergo the necessary CML treatment for the management of second and third generations of TKIs.

The questionnaire was divided into two categories: the first part comprised patients' demographic characteristics, which include sex, age, residency, and chronic disease at time of diagnosis (diabetes mellites, HTN, Hypothyroidism, Asthma and IHD). The second part consisted of duration exposure to imatinib, clinical adverse effects at time of switching, blood characteristic, renal function tests (RFT), liver function tests (LFT), quantitative PCR at time of switching and reason of switching.

First-line treatment began on the date of the first TKI prescription and ended on the date of switching to another TKI, death, last follow-up, or beginning of a Treatment-Free Remission (TRF) period if achieved, which ever event came first. Times to Major Molecular Response (MMR) and other events were calculated in months from TKI initiation. Patients not receiving first-line TKI treatment or treated with hydroxyurea for more than 3 months and those transformed to acute leukemia were excluded. Short pretreatment (<3 months) with interferon alpha or hydroxyurea was allowed. Treatment dosage was not collected in the study and data were most likely not available at a satisfying level in the study population. First-line TKI treatment was split into two groups: the "imatinib group" (IM) for patients treated with imatinib, associated or not with other treatments (i.e., interferon), and the new-generation group" (NG- TKI) for patients treated with dasatinib, ponatinib, bosutinib, or nilotinib. Age was divided into three categories (<30 years old, 30– 65 years old, and >65 years old), with the Eastern Cooperative Oncology Group (ECOG) score split in two (0– 1 and ≥2

Treatment interruption was defined as a gap in treatment of >1 day before restarting the same TKI, from the day the TKI was temporarily discontinued and ending the day before restarting (rr). Treatment discontinuation was defined as cessation of TKI treatment that did not qualify as a treatment interruption; a switch was defined as discontinuation of index TKI, followed by start of second-line TKI during the follow-up period (rr). All patients who switched TKI treatment were considered as having discontinued therapy (rr). Treatment interruptions and discontinuations were analyzed according to the date of TKI discontinuation and TKI switch, according to the date of second-line TKI start. Treatment interruptions and discontinuations were grouped according to whether they occurred within 1 year of index TKI initiation (first year of therapy) or between 1 and 2 years after index TKI initiation (second year of therapy).

Categorical variables were expressed as counts and percentages. Data was collected and tabulated in Microsoft Excel spreadsheets and analyzed using the GraphPad Prism 8.0.

3. RESULTS

Table 1 reports demographic data and the corresponding number of 90 CML patients for various periods of follow-up spanning from 2014 to 2024 for the outpatient clinic of a reference hospitals in Kurdistan Region- Iraq. The highest frequency was found in age groups >50 years, which was 39 (43.33%) followed by 40-50 years 25 (27.78%) and the lowest frequency was found in age <40 years 26(28.89%). Among them, 47(52.22%) were males and 43(47.78%) were females.

The majority of the CML cases were found in Erbil 35(38.89%) followed by Suleimani 29 (32.22%) and the lowest rate was revealed in Duhok City which was 26(28.89%). Patients were grouped into two groups according to the chronic disease at time of diagnosis, The majority of them, 75.56%, had no chronic diseases at the time of diagnosis. Furthermore, Table 2 shows number of patients with different Chronic diseases at time of diagnosis. The highest rate of CML cases was found in D.M 6 (6.67%), followed by HTN 5 (5.56%), and the lowest rate was recorded among other diseases which was 1(1.11%).

Table 1: Demographic data of CML patients

Characteristic		No. Patients	Percentage (%)
Sex	Male	47	52.22
	Female	43	47.78
Ages	<40	26	28.89
	40-50	25	27.78
	>50	39	43.33
Residency	Erbil	35	38.89
	Duhok	26	28.89
	Suleimani	29	32.22
Chronic disease at time of diagnosis	No	68	75.56
	Yes	22	24.44

Table 2: Frequency of chronic diseases at time of diagnosis in CML patients

Chronic diseases at time of diagnosis	No. of Patients	(%)
D.M	6	6.67
D.M. + HTN	1	1.11
Heart failure, HTN, Hypothyroidism	1	1.11
HTN	5	5.56
HTN, Hypothyroidism	1	1.11
HTN, Asthma	1	1.11
Hypothyroidism	1	1.11
IHD, HTN	2	2.22
Ischemic heart disease change it to IHD	1	1.11
Papillary carcinoma of thyroid	1	1.11
Rheumatoid arthritis	1	1.11
SLE	1	1.11

Imatinib was the first signal transduction inhibitor (STI) used in a clinical setting. It prevents a BCR-ABL protein from exerting its role in the oncogenic pathway in CML cases. Results from this study show the outstanding effectiveness of imatinib was highest in 11-20 months, which was 41(45.56%), followed by 1-10 months 19(21.11%) and the lowest rates

was found in 31-40, which was 8(8.89%) As shown in table 3. Furthermore, patients diagnosed with chronic myeloid leukemia (CML) in chronic phase (CP) and treated with imatinib often experience chronic, low-grade adverse events (AEs) that may negatively impact their quality of life and their ability to remain on long-term therapy the clinical adverse effects at time of switching were shown in table 4. The most frequent Imatinib -related AEs (any grade) occurring in 45% of total patients were Diarrhea 10(11.11%), Myalgia 7(7.78%), Epigastric pain 5(5.56%), Multiple skin lesion 4(4.44%), Fatigue 2(2.22%), and ascites, ascites and diarrhea, diarrhea, dysuria, hand numbness, headache and blurred vision, hematuria and urinary tract infection (UTI), lower limb muscle spasm, Multiple skin rash, recurrent upper respiratory tract infection (URTI), Recurrent UTI, severe diarrhea/dyspepsia and severe myalgia with bone pain which was 1(1.11%), respectively.

Table 3: Frequency of Imatinib with Duration exposure at time of switching in CML

Duration exposure to Imatinib/ months	No. of Patients	(%)
1-10	19	21.11
11-20	41	45.56
21-30	11	12.22
31-40	8	8.89
>40	11	12.22

Table 4: Frequency of Imatinib with clinical adverse effects at time of switching in CML (Treatment emergent adverse events).

Clinical adverse effects at time of switching	No. of Patients	(%)
No	49	54.44
Ascites	1	1.11
Ascites and diarrhea	1	1.11
Diarrhea	1	1.11
Dyspepsia	10	11.11
Dysuria	1	1.11
Epigastric pain	5	5.56
Fatigue	2	2.22
Hand numbness	1	1.11
Headache and blurred vision	1	1.11
Hematuria and UTI	1	1.11
Lower limb muscle spasm	1	1.11
Multiple skin rash	1	1.11
Multiple skin lesion	4	4.44
Myalgia	7	7.78
Recurrent URTI	1	1.11
Recurrent UTI	1	1.11
Severe diarrhea/dyspepsia	1	1.11
Severe myalgia+ bone pain	1	1.11

The patients switched from imatinib their WBC was 8.65, with median Hb levels (11.65 g/dl) and the mean and std was (11.62±0.20) and the median platelet count was 193 d/L (ranging from, 6-900 d/L) as shown in table 5.

Table 5: Frequency of Imatinib with blood characteristic

Characteristic of blood	Minimum	Median	Maximum	Mean± Std. error
WBC at time of switching	0.5	8.65	200	17.34±3.535
Hb at time of switching	6.9	11.65	15.1	11.62±0.2015
Platelet, count at time of switching	6	193	900	206±14.44

Regarding the effect of long-term TKI treatment on kidney function and the incidence and prognosis of chronic kidney disease (CKD) in CML patients, 86 (95.56%) have normal renal function tests (RFT) an only 4(4.44%) has increased urea and creatinine. Furthermore, 83 (92.22%) had normal liver function tests and only 1 (1.11%) had elevated total bilirubin, 1(1.11%) increasing 1-fold, 4(4.44%) patients increasing 2 folds and 1(1.11%) increasing 3 folds.

Table 6: Clinical characteristics of patients developed kidney and liver injury in CML patients

Tests		No. of patients	(%)
Renal function tests (RFT)	Normal	86	95.56
	elevated urea and creatinine	4	4.44
Liver function tests (LFT)	Normal	83	92.22
	elevated total bilirubin	1	1.11
	1 fold increased	1	1.11
	2 fold increased	4	4.44
	3 fold increased	1	1.11

Moreover, the quantification was still relative in the majority of labs: in fact, the transcript measured after 3 months of treatment was compared to the measurement initially obtained at diagnosis; the transcript was then measured after 6 months and compared to that of the third month and so on. It was a very difficult and time-consuming approach, especially for physicians. After that, the quantification became obsolete due to the introduction of a reference curve or of specific standards in the PCR reaction, which was definitely a success, but the standardization of the molecular tests was necessary to allow us to compare results derived from different laboratories, thus introducing molecular response as the primary objective of the clinical trials.

Table 7: Reason of switching with second generation in CML patients

Reason of switching	Second generation					
	Nilotinib	(%)	Bosutinib	(%)	Dasatinib	(%)
Drug resistance	47	52.22	8	8.89	1	1.11
Lost follow up	2	2.22	0	0.00	0	0.00
Lost response to Imatinib	14	15.56	3	3.33	0	0.00
Acute leukemia transformation	5	5.56	0	0.00	1	1.11
Drug intolerance/Side effect	6	6.67	3	3.33	0	0.00
Total	74	82.22	14	15.56	2	2.22

4. DISCUSSION

In this study, we observed a slight male predominance among CML patients, consistent with the findings of Cortes et al.[13] and Gorre et al.[14] . This trend may be attributed to greater occupational or environmental exposures among men in our region, potentially increasing their risk of CML. However, our results differ from those of Hoglund et al.[15] , who reported a slight female predominance, suggesting that gender distribution in CML may vary across populations and study designs.

On the other hand, our analysis found that there has been a marked increase in use of TKIs in patients aged over 51 years, as evidenced by 43.33% of included CML patients initiating TKI therapy. The result corresponding with (14)which found to be highly prevalent in the age groups of 20–40 years (58.8%) and >40 years (33.8%), confirming that mostly middle-aged

people had higher risk to develop CML. Furthermore, Osho et al (16) confirming that mostly middle-aged people had higher risk to develop CML. Similar age distribution was seen in the study in Nigeria.

The majority of the CML cases were found in Erbil 35(38.89%) followed by Suleimani 29 (32.22%) and the lowest rate was revealed in Duhok city which was 26(28.89%) as shown in table 1. The result agreed with Vojdani et al (17) reported that, pesticide exposure and other chemical toxicity (18) affected the functioning of the blood vascular system, and improper use of pesticides and chemical toxicity was shown to induce neurological and hematological complications in individuals, (19, 20)which might be the reason for enhanced risk of CML development among population.

Introduction of imatinib (Glivec, Novartis) into clinical practice nearly one decade ago, has dramatically changed treatment and follow-up of CML. Imatinib specifically targets tyrosine kinase activity of the oncogenic protein encoded by BCR/ABL gene. Subsequently, other tyrosine kinase inhibitors (TKIs) were developed. Currently, two other TKIs are available for clinical use, namely dasatinib (Sprycel, Bristol-Myers Squibb) and nilotinib (Tasigna, Novartis) BUYUKASIK (21). Furthermore, the treatment of CML must be individualized based on the presence of other chronic diseases at the time of diagnosis. Close monitoring and collaboration between oncologists and specialists in other fields (cardiology, nephrology, pulmonology, endocrinology) are crucial to optimize treatment outcomes and minimize complications (22).

Table 3 shows the effectiveness of imatinib was highest in 11-20 months which was 41(45.56%), followed by 1-10 months 19(21.11%) and the lowest rates was found in 31-40 months which was 8(8.89%). Each of the TKIs approved for the treatment of patients with CML-chronic phase has a distinct toxicity profile that should be carefully considered when prescribing TKI treatment. It is now well known that first- (imatinib) and second- (dasatinib, nilotinib) generation TKIs act on different molecular targets (23), and that their side effects are mainly due to the inhibition not only of BCR-ABL1, but also of other tyrosine kinases such as c-kit, PDGFR, *Src* or $EPHB_4$ (24).

Table 4 shows the appearance of clinical signs and symptoms related to the disease at the time of treatment with Imatinib Or they were the side effect of the treatment. The main presenting symptom were dyspepsia 10 (11.11%) and myalgia 7(7.78%), epigastric pain 5(5.56%), multiple skin lesion 4(4.44) and fatigue 2(2.22). Other signs and symptoms include ascites, ascites and diarrhea, diarrhea, dysuria, hand numbness, headache and blurred vision, hematuria and UTI, lower limb muscle spasm, multiple skin rash, recurrent UTI, severe diarrhea/dyspepsia and severe myalgia+ bone pain 1(1.11). Imatinib mesylate is presently considered as first-line treatment in CML patients. Imatinib is a small molecule tyrosine kinase inhibitor targeting specific BCR-ABL kinase, the tolerability is good with fewer adverse events compared with other cytotoxic anticancer agents (25). The adverse events mostly occur during the initial stage of therapy, and their extent depends on the phase of the disease and the dose given (22).

Hematologic response to Imatinib must be evaluated every 2 weeks before complete hematologic response as defined by white cells count, differential without immature granulocytes, basophils and platelet count. The results correspond to Shoukier et al (26) which revealed that, the most common hematologic adverse events of Imatinib to patients with chronic phase CML were anemia, thrombocytopenia, and neutropenia and none of patients stopped the treatment because of adverse events. On the other hand, both the efficacy and toxicity of TKIs are dependent on the plasma concentrations of the drugs (27, 28). However, the plasma concentrations of TKIs are affected by concomitantly administered drugs and the functions of the liver and kidneys, which are involved in drug absorption, metabolism, and excretion. Thus, special attention should be paid to patients who are taking multiple drugs or that have organ dysfunction when prescribing TKIs (29).

The management of adverse drug reactions that occurred in the study was treated according to the previously published guidelines (30). The management of the adverse drug reactions usually involves temporary cessation of imatinib usually in the case of Grade III and Grade IV hematological toxicities. Dose modification was warranted for a few patients due to persistent hematologic toxicities. Most of the adverse drug reactions were encountered during the initial 3 months of the imatinib treatment, which is in accordance with studies published elsewhere.(31). None of the patients were discontinued from imatinib therapy due to toxicities (32). Furthermore, second generation TKIs are associated with excellent clinical outcomes (33, 34). Indeed, these drugs have become important options in the front-line therapy of CML (35). However, TKI therapy is known to be associated with toxicity, leading to a switch in therapy for a significant minority of patients (36, 37). Yet, the clinical outcome of patients who switch from upfront therapy with a second generation TKIs (2GTKI) to an alternative TKI has not been well described, with the exception of those who develop a BCR-ABL kinase domain mutation that guides subsequent TKI therapy (38, 39).

5. CONCLUSION

The use of tyrosine kinase inhibitors (TKIs) has revolutionized the treatment of chronic myeloid leukemia (CML), making it possible for patients to have a life expectancy similar to that of the healthy population. To improve treatment adherence and effectiveness, it is necessary to understand the side effects that the medications may cause. On the other hand, the importance of TKI discontinuation studies are strengthened by recognition of long-term adverse events. Patients were divided into two groups based on the chronic disease they had at the time of diagnosis. 75.56%, of the patients had no chronic diseases at the time of diagnosis. Six patients had the greatest rate of CML cases with D.M, followed by HTN,

and the lowest rate was recorded among other diseases which was 1(1.11%). The most frequent Imatinib -related AEs (any grade) occurring in 45% of total patients were diarrhea, myalgia, epigastric pain, multiple skin lesion, fatigue, and ascites. The most common hematologic adverse events of imatinib to patients with chronic phase CML were anemia and thrombocytopenia and none of patients stopped the treatment because of adverse events. Regarding the effect of long-term TKI treatment on kidney and liver function, only 4(4.44%) has increased urea and creatinine and 1(1.11%) had elevated total bilirubin. It is apparent that failure of 1L-TKI is a challenging problem in modern CML therapy. Intolerance can be effectively managed by switching to an alternative 2GTKI, but resistance requires early consideration of 3/4GTKI.

REFERENCES

[1] Miranda-Filho A, Piñeros M, Ferlay J, Soerjomataram I, Monnereau A, Bray F. Epidemiological patterns of leukaemia in 184 countries: a population-based study. The Lancet Haematology. 2018;5(1):e14-e24.

[2] Thompson PA, Kantarjian HM, Cortes JE, editors. Diagnosis and treatment of chronic myeloid leukemia in 2015. Mayo Clinic Proceedings; 2015: Elsevier.

[3] Donato NJ, Wu JY, Stapley J, Lin H, Arlinghaus R, Aggarwal B, et al. Imatinib mesylate resistance through BCR-ABL independence in chronic myelogenous leukemia. Cancer research. 2004;64(2):672-7.

[4] Kantarjian HM, Giles F, Gattermann N, Bhalla K, Alimena G, Palandri F, et al. Nilotinib (formerly AMN107), a highly selective BCR-ABL tyrosine kinase inhibitor, is effective in patients with Philadelphia chromosome–positive chronic myelogenous leukemia in chronic phase following imatinib resistance and intolerance. Blood, The Journal of the American Society of Hematology. 2007;110(10):3540-6.

[5] Cortes JE, Kantarjian HM, Brümmendorf TH, Kim D-W, Turkina AG, Shen Z-X, et al. Safety and efficacy of bosutinib (SKI-606) in chronic phase Philadelphia chromosome–positive chronic myeloid leukemia patients with resistance or intolerance to imatinib. Blood, The Journal of the American Society of Hematology. 2011;118(17):4567-76.

[6] Jabbour E, Kantarjian H, Cortes J. Use of second-and third-generation tyrosine kinase inhibitors in the treatment of chronic myeloid leukemia: an evolving treatment paradigm. Clinical Lymphoma Myeloma and Leukemia. 2015;15(6):323-34.

[7] Canet J, Cony-Makhoul P, Orazio S, Cornet E, Troussard X, Maynadié M, et al. Second-or third-generation tyrosine kinase inhibitors in first-line treatment of chronic myeloid leukemia in general population: Is there a real benefit? Cancer Medicine. 2021;10(20):6959-70.

[8] Mersin S, Gülük F, Gülcan E, Eşkazan AE. Current and emerging tyrosine kinase inhibitors for the treatment of chronic myeloid leukemia in young adults. Expert Opinion on Pharmacotherapy. 2023;24(15):1703-13.

[9] Iriyama N, Iwanaga E, Kimura Y, Watanabe N, Ishikawa M, Nakayama H, et al. Changes in chronic myeloid leukemia treatment modalities and outcomes after introduction of second-generation tyrosine kinase inhibitors as first-line therapy: a multi-institutional retrospective study by the CML Cooperative Study Group. International Journal of Hematology. 2024:1-11.

[10] Chitanava T, Matvienko I, Shuvaev V, Voloshin S, Martynkevich I, Vlasova Y, et al. Long-term outcomes of third-line therapy with tyrosine kinase inhibitors in chronic phase chronic myeloid leukemia: A real-life experience. Frontiers in Oncology. 2023;13:1138683.

[11] El Fakih R, Chaudhri N, Alfraih F, Rausch CR, Naqvi K, Jabbour E. Complexity of chronic-phase CML management after failing a second-generation TKI. Leukemia & Lymphoma. 2020;61(4):776-87.

[12] Qian H, Gang D, He X, Jiang S. A review of the therapeutic role of the new third-generation TKI olverembatinib in chronic myeloid leukemia. Frontiers in Oncology. 2022;12:1036437.

[13] Cortes J, Pavlovsky C, Saußele S. Chronic myeloid leukaemia. The Lancet. 2021;398(10314):1914-26.

[14] Gorre M, Sashidhar R, Annamaneni S, Digumarti R, Satti V. Demographic and clinical characteristics of chronic myeloid leukemia patients: A study on confined populations of Southern India. Indian Journal of Medical and Paediatric Oncology. 2019;40(S 01):S70-S6.

[15] Höglund M, Sandin F, Simonsson B. Epidemiology of chronic myeloid leukaemia: an update. Annals of hematology. 2015;94:241-7.

[16] Osho P, Aneke J, Ojo M, Onoja A, Oni T. Clinical and Laboratory Features of Nigerian Patients with Chronic Myeloid Leukaemia: A Cohort Study. Western Journal of Medical and Biomedical Sciences. 2022;3(2):43-8.

[17] Vojdani A, Ghoneum M, Brautbar N. Immune alteration associated with exposure to toxic chemicals. Toxicology and industrial health. 1992;8(5):239-54.

[18] Lamm SH, Engel A, Joshi KP, Byrd III DM, Chen R. Chronic myelogenous leukemia and benzene exposure: A systematic review and meta-analysis of the case–control literature. Chemico-biological interactions.

2009;182(2-3):93-7.

[19] Burke RD, Todd SW, Lumsden E, Mullins RJ, Mamczarz J, Fawcett WP, et al. Developmental neurotoxicity of the organophosphorus insecticide chlorpyrifos: from clinical findings to preclinical models and potential mechanisms. Journal of neurochemistry. 2017;142:162-77.

[20] Laporte B, Gay-Quéheillard J, Bach V, Villégier A-S. Developmental neurotoxicity in the progeny after maternal gavage with chlorpyrifos. Food and Chemical Toxicology. 2018;113:66-72.

[21] Buyukasik Y, Haznedaroglu IC, Ilhan O. Chronic myeloid leukemia: Practical issues in diagnosis, treatment and follow-up. International Journal of Hematology and Oncology. 2010;33(1):001-12.

[22] Osman AE, Deininger MW. Chronic Myeloid Leukemia: Modern therapies, current challenges and future directions. Blood reviews. 2021;49:100825.

[23] Baccarani M, Deininger MW, Rosti G, Hochhaus A, Soverini S, Apperley JF, et al. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. Blood, The Journal of the American Society of Hematology. 2013;122(6):872-84.

[24] Iurlo A, Orsi E, Cattaneo D, Resi V, Bucelli C, Orofino N, et al. Effects of first-and second-generation tyrosine kinase inhibitor therapy on glucose and lipid metabolism in chronic myeloid leukemia patients: a real clinical problem? Oncotarget. 2015;6(32):33944.

[25] Sacha T. Imatinib in chronic myeloid leukemia: an overview. Mediterranean journal of hematology and infectious diseases. 2014;6(1):e2014007.

[26] Shoukier M, Borthakur G, Jabbour E, Ravandi F, Garcia-Manero G, Kadia T, et al. The effect of eltrombopag in managing thrombocytopenia associated with tyrosine kinase therapy in patients with chronic myeloid leukemia and myelofibrosis. Haematologica. 2020;106(11):2853.

[27] Sohn SK, Oh SJ, Kim BS, Ryoo HM, Chung JS, Joo YD, et al. Trough plasma imatinib levels are correlated with optimal cytogenetic responses at 6 months after treatment with standard dose of imatinib in newly diagnosed chronic myeloid leukemia. Leukemia & Lymphoma. 2011;52(6):1024-9.

[28] Dorer DJ, Knickerbocker RK, Baccarani M, Cortes JE, Hochhaus A, Talpaz M, et al. Impact of dose intensity of ponatinib on selected adverse events: multivariate analyses from a pooled population of clinical trial patients. Leukemia research. 2016;48:84-91.

[29] Taniguchi Y, Takahashi N, Miura M, Hirase C, Sueda S, Espinoza JL, et al. The impact of hemodialysis and liver cirrhosis on the plasma concentrations of tyrosine kinase inhibitors in a patient with chronic myeloid leukemia. Internal Medicine. 2020;59(21):2745-9.

[30] Breccia M, Colafigli G, Molica M, Alimena G. Adverse events associated with tyrosine kinase inhibitors for the treatment of chronic myeloid leukemia. Expert Opinion on Drug Safety. 2016;15(4):525-33.

[31] Phukan A, Mandal PK, Dolai TK. Efficacy and safety profile of generic imatinib in patients with newly diagnosed chronic myeloid leukemia-chronic phase: sharing experience of a hemato-oncology center from eastern India. Annals of Hematology. 2021;100(1):85-96.

[32] Francis J, Palaniappan M, Dubashi B, Pradhan SC, Chandrasekaran A. Adverse drug reactions of imatinib in patients with chronic myeloid leukemia: A single-center surveillance study. Journal of Pharmacology and Pharmacotherapeutics. 2015;6(1):30-3.

[33] Cortes JE, Saglio G, Kantarjian HM, Baccarani M, Mayer J, Boqué C, et al. Final 5-year study results of DASISION: the dasatinib versus imatinib study in treatment-naïve chronic myeloid leukemia patients trial. Journal of Clinical Oncology. 2016;34(20):2333-40.

[34] Franke G-N, Maier J, Wildenberger K, Cross M, Giles FJ, Müller MC, et al. Comparison of real-time quantitative PCR and digital droplet PCR for BCR-ABL1 monitoring in patients with chronic myeloid leukemia. The Journal of Molecular Diagnostics. 2020;22(1):81-9.

[35] Shah NP. Front-line treatment options for chronic-phase chronic myeloid leukemia. Journal of Clinical Oncology. 2018;36(3):220-4.

[36] Steegmann JL, Baccarani M, Breccia M, Casado L, García-Gutiérrez V, Hochhaus A, et al. European LeukemiaNet recommendations for the management and avoidance of adverse events of treatment in chronic myeloid leukaemia. Leukemia. 2016;30(8):1648-71.

[37] Chow EJ, Doody DR, Wilkes JJ, Becker LK, Chennupati S, Morin PE, et al. Adverse events among chronic myelogenous leukemia patients treated with tyrosine kinase inhibitors: a real-world analysis of health plan enrollees. Leukemia & lymphoma. 2021;62(5):1203-10.

[38] Cortes JE, Kim D-W, Pinilla-Ibarz Jl, Le Coutre P, Paquette R, Chuah C, et al. A phase 2 trial of ponatinib in

Philadelphia chromosome–positive leukemias. New England Journal of Medicine. 2013;369(19):1783-96.

[39] Ma C-E, Ghosh S, Leyshon C, Blosser N, Dersch-Mills D, Jupp J, et al. Clinical outcome of chronic myeloid leukemia patients who switch from first-line therapy with a second generation tyrosine kinase inhibitor to an alternative TKI. Leukemia research. 2021;111:106674.