Bull. Pharm. Sci., Assiut University, Vol. 47, Issue 2, 2024, pp. 1177-1188.

Bulletin of Pharmaceutical Sciences
Assiut University
Website: http://bpsa.journals.ekb.eg/

BULL. PHARM. SCI. Assiut Univ.

NILOTINIB VS IMATINIB IN PATIENTS WITH NEWLY DIAGNOSED CHRONIC MYELOID LEUKEMIA-CHRONIC PHASE

A. M. Morsy[*1], H. H. Essa[1], A. F. Amin[1], J. G. Maxwell[2], D. A. Gamal[1]

[1]*Clinical Oncology Department, Faculty of Medicine, Assiut University, Egypt*
[2]*Suhag Health Insurance Hospital, Egypt*

Chronic myeloid leukemia (CML) is a progressive blood cancer effectively treated with BCR-ABL1 tyrosine kinase inhibitors (TKIs) nilotinib and imatinib. ***Objectives:*** *This study compares their efficacy in newly diagnosed CML-CP patients.* ***Methods:*** *Ninety-two patients were divided into two groups: 46 received imatinib 400 mg once daily, and 46 received nilotinib 300 mg BID. Evaluations, including history, physical examinations, and laboratory tests, were conducted every three months over three years. Molecular responses were assessed using RQ-PCR.* ***Results:*** *Anemia occurred in 13% of the Nilotinib group and 22% of the Imatinib group, leucopenia in 13% of both groups, and thrombocytopenia in 0% of the Nilotinib group versus 8% of the Imatinib group. Nilotinib showed significantly better progression-free survival and five-year survival rates.* ***Conclusion:*** *nilotinib demonstrated a more immediate and profound molecular response, improved survival chances, and fewer adverse effects, making Nilotinib 300 mg BID recommended as the first-line treatment for newly diagnosed CML-CP patients.*

Keywords: *Nilotinib, Imatinib, Chronic Myeloid Leukemia*

INTRODUCTION

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm characterized by the presence of the Philadelphia chromosome, a translocation between chromosomes 9 and 22, which creates the BCR-ABL fusion gene. This gene encodes for a constitutively active tyrosine kinase responsible for the uncontrolled proliferation of leukemic cells [1]. The treatment landscape of CML has been revolutionized over the past two decades by the advent of tyrosine kinase inhibitors (TKIs), with imatinib being the first such drug introduced in 2001 [2]. Imatinib transformed CML-CP management by offering improved survival rates and disease control compared to prior therapies, achieving a five-year survival rate of nearly 90% [3]. Despite its success, around 30-40% of patients develop resistance or intolerance to imatinib, which underscores the need for alternative TKIs [4].

Nilotinib, a second-generation TKI, was developed to address the limitations of imatinib. It exhibits greater potency and specificity for the BCR-ABL kinase, as well as activity against several imatinib-resistant BCR-ABL mutations [5]. Studies have consistently shown that nilotinib induces faster and deeper molecular responses compared to imatinib, which may translate into improved long-term outcomes [6]. In the landmark ENESTnd trial, nilotinib significantly increased the rates of major molecular response (MMR) and complete cytogenetic response (CCyR) in patients with newly diagnosed CML-CP, as well as reduced the risk of progression to advanced phases of the disease [7]. The 10-year follow-up data from this trial further highlighted nilotinib's superior efficacy, demonstrating sustained molecular response and an overall favorable survival profile [4].

Safety considerations are essential in comparing these two TKIs. While nilotinib offers enhanced efficacy, it has been associated

Received : 24/7/2024 & Accepted : 6/11/2024

*Corresponding author: A. M. Morsy, E-mail: dr_aiat@aun.edu.eg

with a distinct side effect profile, including an increased risk of cardiovascular events such as arterial occlusive diseases. This has led to ongoing discussions about balancing the therapeutic benefits of nilotinib with potential long-term risks, particularly in patients with pre-existing cardiovascular conditions [8].

Given the evolving landscape of CML treatment, this study aims to comprehensively compare nilotinib and imatinib in newly diagnosed CML-CP patients.

PATIENTS AND METHODS

Study Design

This study is a prospective follow up study conducted at the clinical Oncology Department, Sohag Cancer center, from January 2020 to January 2024. Ninety-two patients with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP), positive for the Philadelphia chromosome (Ph+ or Ph– BCR-ABL1+), were included. These patients were divided into two groups: Group I (46 patients) received Imatinib 400 mg once daily, and Group II (46 patients) received Nilotinib 300 mg twice daily.

Patient Enrollment

Patients were enrolled in the study based on a confirmed diagnosis of newly diagnosed CML-CP. Patients with accelerated or blast-phase CML or those receiving treatment prior to the study were excluded. Treatment was determined by the treating physician, taking into account patient characteristics such as age, medical history, and clinical presentation.

Ethical Approval and Consent

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki. Ethical approval was obtained from the Institutional Review Board (IRB) of the Faculty of Medicine, Assiut University, prior to patient enrollment (IRB local approval number 17200099). All patients provided written informed consent after being thoroughly informed of the study's objectives, procedures, potential risks, and benefits.

Follow-up and Data Collection

Patients were followed up every three months over the course of the study period. At each visit, a thorough medical history was taken, along with physical examinations and laboratory investigations. Molecular responses were assessed at these intervals using quantitative real-time polymerase chain reaction (RQ-PCR) for BCR-ABL1 transcripts. The primary efficacy endpoint was the achievement of major molecular response (MMR) at 3, 6, 12, and 24 months. Additionally, overall survival (OS) and progression-free survival (PFS) were monitored every three months, and adverse events were documented at each follow-up visit.

Molecular Response Assessment

Molecular response was evaluated every three months using RQ-PCR to quantify the ratio of BCR-ABL1 transcripts relative to control genes (ABL) based on the International Scale (IS). All molecular testing was performed in the Clinical Oncology Department's specialized laboratory.

Adverse Event Monitoring

Adverse effects were closely monitored throughout the study. These were categorized based on clinical symptoms and laboratory test abnormalities and graded according to standardized criteria. Adverse effects were assessed every three months at each patient follow-up, and any side effects, including cardiovascular events or hematological abnormalities, were recorded.

Sample size calculation

The sample size for this study was determined using the following equation based on detecting a significant difference in molecular response rates between the two treatment groups (Nilotinib and Imatinib):

$$n = Z(\alpha/2)^2 * p(1-p) / d^2$$

Where:
- $Z(\alpha/2)$ is the critical value of the standard normal distribution at a 95% confidence level (1.96),
- p is the estimated proportion of molecular response based on Hochhaus et al.[9] study (assumed to be 0.5 for maximum variability),
- d is the desired margin of error (set at 0.1).

Based on this equation, we calculated a minimum sample size of 46 patients per group

to detect a clinically significant difference with 80% power.

Data Management and Statistical Analysis

All patient data were entered into a secure clinical database and managed in accordance with best practices for data integrity and confidentiality. Manual and visual data checks were conducted to ensure accuracy.

Statistical analyses were conducted using STATA software (version 14.2, StataCorp, TX). Numerical data were expressed as mean, median, and standard deviation. Comparative analyses between the two treatment groups were performed using t-tests for normally distributed variables and Mann-Whitney U tests for non-normally distributed variables. Kaplan-Meier curves were generated for survival analysis, and statistical significance was defined as a p-value of less than 0.05.

RESULTS AND DISCUSSION

Results

Ninety Two cases were enrolled in this study as recentry diagnosed chronic myeloid leukemia – chronic phase. There were a total of 46 patients enrolled in the Nilotinib group and 46 patients enrolled in the Imatinib group over the course of the study's three-year follow-up period. There were no patient or study-related losses or deaths. Both the Imatinib and Nilotinib groups included people of varying ages (20-78 and 20-65, respectively). In both groups, males made up the majority. Neither group differed significantly from the other in terms of age, gender, ECOG >1, Hb level, Platelet count, WBC count, Blastocyst cells in peripheral blood (BP) Eosinophil cells in PB, Basophils cells in PB Spleen length, palpable spleen and Sokal score as shown in **table 1**.

Table 1: Patients characteristics at diagnosis.

Variable	Imatinib (400mg) N=46	Nilotinib (150mg) N=46	P value
Age by years; Median (range)	49 (20-78)	42.5 (20-65)	0.08
Gender; Male/female	26/20	26/20	0.99
ECOG ≥1, N%	100%	100%	0.99
Hb level, g/dl; median (range)	10.3 (7.0:13.2)	9.4 (7.3: 12.2)	0.06
Platelet count, 10^9/L; median (range)	150.0 (55:301)	120.5 (66:301)	0.22
WBC count, 109/L; median (range)	11.0 (2.3:335.0)	6.4 (2.8:799)	0.01
Blast cells in PB, % median (range)	1.0 (0:13)	1.0 (0:14)	0.95
Eosinophis cells in PB, % median (range)	2.0 (0:10)	2.0 (0: 12)	0.95
Basophils cells in PB, % median (range)	2.1 (0:12)	2.2 (0:13)	0.84
Spleen, cm; Median (range)	1 (0:23)	1 (0:25)	0.99
Palpable spleen, N (%)	22 (48%)	20 (43%)	0.632
Sokal score, N(%)			0.89
Low	22 (48%)	23 (50%)	
Intermediate	20 (43%)	18 (39%)	
High	4 (9%)	5 (11%)	

'BCR-ABL1IS'**:** BCR-ABL/ABL% ratio, according to the Global Positioning System. The response rates were calculated by simply dividing the total of the patients who had that reaction at the time by cumulative patient count recruited in each arm (N=46). In **table 2**, we display the MMR, MR4, and MR4.5 prevalence rates at 3, 6, 12, 18, 24, and 36 months. At 3 months, Nilotinib group 24% of patients were in MMR, 2% were in MR4, and 0% were in MR4.5. While in Imatinib group 23% of patients were in MMR, 2% were in MR4, and 0% were in MR4.5. without any discernible distinction between the two categories. Half of individuals treated with Nilotinib at 6 months were in MMR, 5% in MR4, and 22% in MR4.5. Patients in the imatinib group were more likely to be in MMR (53 percent), MR4 (12 percent), and MR4.5 (2 percent) (P = 0.2). At 12 months, Nilotinib group 21% of patients were in MMR, 32% were in MR4, and 45% were in MR4.5. While in Imatinib group 57% of patients were in MMR, 28% were in MR4, and only 7% were in MR4.5 (P = 0.01). At 18 months, Nilotinib group 18% of patients were in MMR, 30% were in MR4, and 52% were in MR4.5. While in Imatinib group 53% of patients were in MMR, 31% were in MR4, and only 21% were in MR4.5 (P < 0.001). At 24 months, Nilotinib group 10% of patients were in MMR, 22% were in MR4, and 66% were in MR4.5. While in Imatinib group 25% of patients were in MMR, 46% were in MR4, and only 27% were in MR4.5 (P < 0.001). At 36 months, Nilotinib group 8% of patients were in MMR, 12% were in MR4, and 80% were in MR4.5. While in Imatinib group 35% of patients were in MMR, 32% were in MR4, and only 32% were in MR4.5 (P < 0.001). Nilotinib outperformed Imatinib when comparing response types.

Regarding hematological adverse effects in **table 3**, With a Hb level under 10%, anemia was diagnosed. There were 6 (13% of the total) cases of anemia in the Nilotinib group and 10 (22% of the total) cases in the Imatinib group (P = 0.40). Three (13% of the whole) patients in each group experienced leucopenia (total leukocyte count (TLC) < 3 10^3/ml; P = 0.76). Patients in the Imatinib group experienced thrombocytopenia (platelets 100 103/ml) on four occasions (P = 0.12), but those in the Nilotinib group did not.

Table 2: Molecular response at milestone.

BCR-ABL^{IS}	Nilotinib Group (n=46)	Imatinib Group (n=46)	P value
At the 3rd month			0.07
≤0.1%	24%	23%	
≤0.01%	2%	2%	
≤0.0032%	0%	0%	
At the 6th month			
≤0.1%	50%	53%	0.001
≤0.01%	15%	12%	
≤0.0032%	22%	2%	
At the 12th month			
<0.1%	21%	57%	<0.001
<0.01%	32%	28%	
<0.0032%	45%	7%	
At the 18th month			
≤0.1%	18%	53%	<0.001
≤0.01%	30%	31%	
≤0.0032%	52%	21%	
At the 24th month			
≤0.1%	10%	25%	<0.001
≤0.01%	22%	46%	
≤0.0032%	66%	27%	
At the 36th month			
≤0.1%	8%	35%	<0.001
≤0.01%	12%	32%	
≤0.0032%	80%	32%	

Table 3: Hematological adverse reactions of therapy in both patient populations.

side effects	Nilotinib (400mg) N=46	Imatinib (150mg) N=46	P value
▪ Anemia	6 (13%)	10 (22%)	0.41
▪ Leucopenia	6 (13%)	6 (13%)	0.76
▪ Thrombocytopenia	0	4 (8%)	0.12

Non-hematological adverse effects revealed no discernible changes between the Nilotinib and Imatinib groups statistically. with 13 (28%) and 4 (9%) patients experiencing Grade 1 and 2 myalgia in the Nilotinib group, and 11 (24%) and 13 (28%) patients experiencing the same in the Imatinib group, respectively (P = 0.053). No patients in the Nilotinib group experienced a rash, while 11 (24%), 4 (9%), and 6 (13%) patients in the Imatinib group experienced a G1, G2, or G3 rash, respectively (P0.001). The incidence of nausea was greater in the Imatinib group than in the Nilotinib group (P = 0.002). Twenty (44%) and eight (16%) of those who took Imatinib experienced G1 and G2 nausea, while only fifteen (32%) of those who took Nilotinib experienced G1.It was a big deal, with a p-value of 0.002. Imatinib patients were more likely to have fatigue, with 28 (61%) and 3 (6%), respectively, experiencing G1 and G2 fatigue. As for the Nilotinib group, just 22% of those taking it and 12% of those taking a placebo had G1 or G2 fatigue, respectively. The two groups were vastly different from one another in terms of diarrhea occurrence (P = 0.031), with the Nilotinib group having a higher frequency of diarrhea (32% vs. 28%). This difference was driven primarily by an increase in the number of patients experiencing G1 and G2 diarrhea (32% vs. 12%) as shown in **table 4**.

Table 4: Therapy-related non-hematological negative consequences in both groups.

side effects	Imatinib (400mg) N=46	Nilotinib (150mg) N=46	P value
Myalgia			0.053
▪ Absent	22 (48%)	29 (63%)	
▪ G1	11 (24%)	13 (28%)	
▪ G2	13 (28%)	4 (9%)	
Rash			**<0.001**
▪ Absent	25 (54%)	46 (100%)	
▪ G1	11 (24%)	0	
▪ G2	4 (9%)	0	
▪ G3	6 (13%)	0	
Nausea			0.002
▪ Absent	18 (40%)	31 (68%)	
▪ G1	20 (44%)	15 (32%)	
▪ G2	8 (16%)	0	
fatigue			0.001
▪ Absent	15 (33%)	30 (66%)	
▪ G1	28 (61%)	10 (22%)	
▪ G2	3 (6%)	6 (12%)	
Diarrhea			0.031
▪ Absent	33 (72%)	26 (56%)	
▪ G1	13 (28%)	15 (32%)	
▪ G2	0	6 (12%)	

At the outset, neither group had a noticeably higher EF than the other. At 6 and 12 months of follow up, in spite of this, the two groups' EFs were distinguishable at the 0.05 level of significance (p=0.02 and 0.0001, respectively) as shown in **Fig. 1**.

P=0.0001 indicated a statistically important distinction within the two groups receiving treatment pertaining to progression-free survival at 5 years. In addition, the results of the 5-year survival rate were significantly different (P=0.011) between the two therapy groups as shown in **Fig. 2&3**.

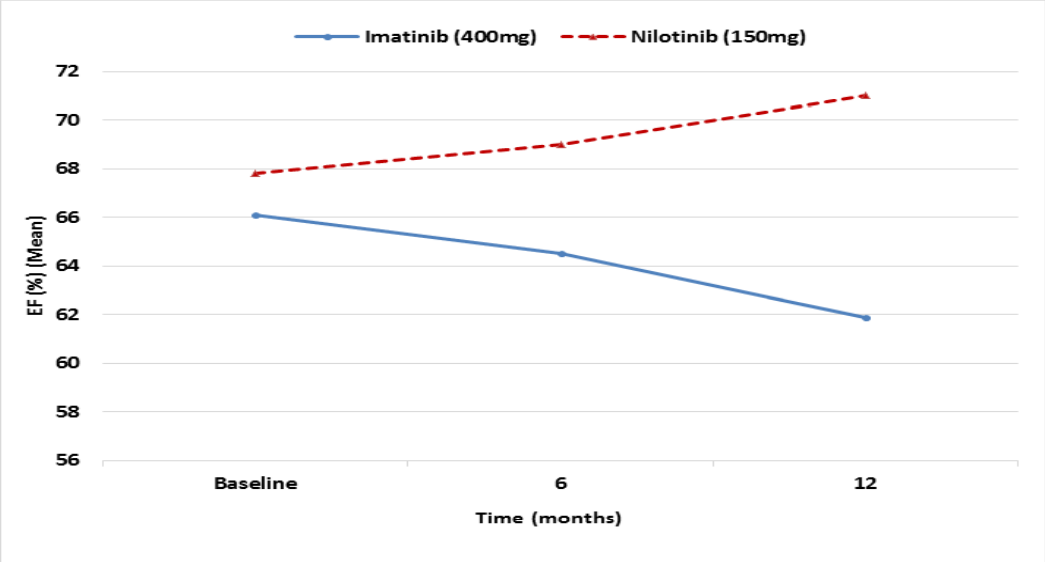

Fig. 1: Comparison between patients treated with Imatinib and those treated with Nilotinib as regards EF (%).

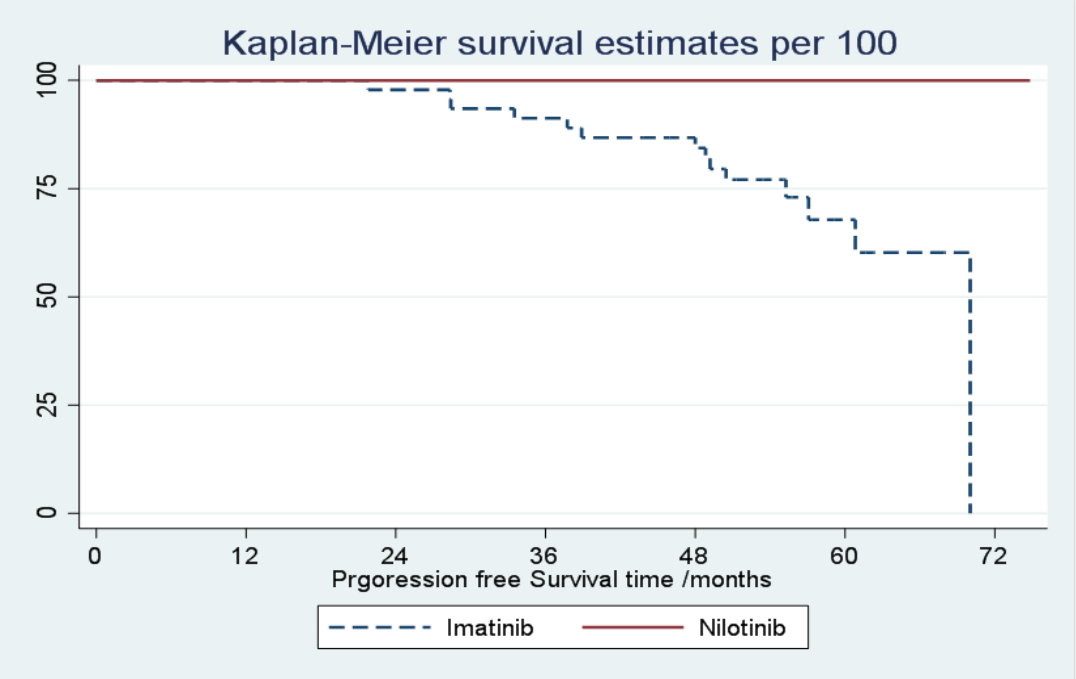

Fig. 2: Comparison between patients treated with Imatinib and those treated with Nilotinib as progression free survival.

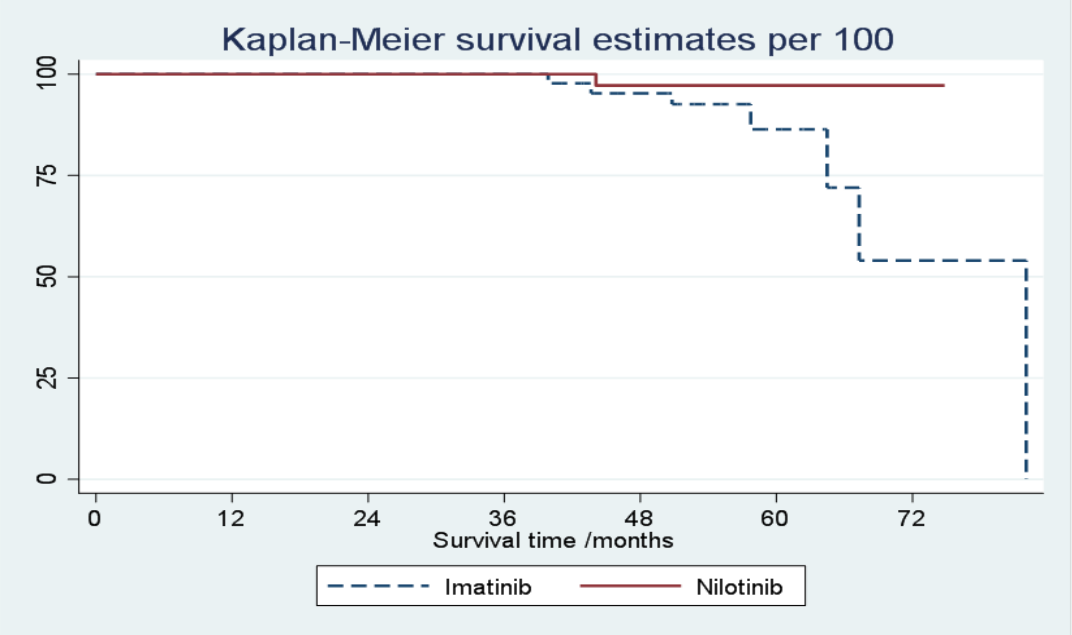

Fig. 3: Comparison between patients treated with Imatinib and those treated with Nilotinib as survival rate.

Discussion

Tasigna (nilotinib) and Gleevec (imatinib) are two tyrosine kinase inhibitors (TKIs) for BCR-ABL1 that was recently recognized for use in treating recently diagnosed patients with CML-CP [10].

We aimed to compare between Nilotinib versusc Imatinib in recently diagnosed cases with CML-Chronic Phase by: Using deep molecular response {which is assessed using RQ-PCR and is expressed primarily according to the proportion of BCR-ABL1 transcripts to ABL transcripts or transcripts of some alternative globally recognized control gene (BCR-ABL1%) based upon the International Scale (IS).

Regarding MMR at 3 months, Class of Nilotinib the MMR percentage was 24%, the MR4 percentage was 2%, and the MR4.5 percentage was 0%. As there isn't a significantly higher percentage of patients in the Imatinib group (23%) received treatment were in MMR, 2% in MR4, and 0% in MR4.5.

Patients with chronic phase CML (CML-CP) who have maintained a deep molecular response (DMR) after receiving frontline nilotinib for more than three years are the focus of ENEST freedom [11].

Significant molecular reaction (MMR; BCR-ABL1 0.1% on the IS [BCRABL1IS]) or better was maintained by 51.6% of patients in the primary analysis 48 weeks after treatment discontinuation. After 96 weeks of TFR, 48.9% of patients were still in MMR. Restarting nilotinib treatment resulted in a reversal of MMR loss in 98.9% of patients and a reversal of MR4.5 loss in 92.0% (described as BCR-ABL1IS 0.0032%). During TFR, the incidence of most AEs decreased over time [12]. It is important to highlight that the median duration of prior nilotinib exposure in this trial was 3.5 years, which is significantly lower than the medians reported in other TKI studies [13, 14].

In our present study, Regarding MMR at 12 months, Nilotinib group 21% of patients were in MMR, 32% were in MR4, and 45% were in MR4.5. While in Imatinib group 57% of patients were in MMR, 28% were in MR4, and only 7% were in MR4.5 (P = 0.01), at 18 months, Nilotinib group 18% of patients were in MMR, 30% were in MR4, and 52% were in MR4.5. While in Imatinib group 53% of patients were in MMR, 31% were in MR4, and only 21% were in MR4.5 (P < 0.001), At 24 months, Nilotinib group 10% of patients were in MMR, 22% were in MR4, and 66% were in MR4.5. While in Imatinib group 25% of patients were in MMR, 46% were in MR4, and only 27% were in MR4.5 (P < 0.001), at 36 months, Nilotinib group 8% of patients were in MMR, 12% were in MR4, and 80% were in MR4.5. While in Imatinib group 35% of patients were in MMR, 32% were in MR4, and only 32% were in MR4.5 (P < 0.001). P 0.001

indicated There was a remarkably substantial distinction between the Nilotinib and Imatinib groups, statistically speaking, with the difference favoring Nilotinib.

In the same context, Kantarjian *et al.,* [15] who investigated patients within the core phase, Patients who had recently been diagnosed with CML-CP were split into three groups and given one of three different treatments at random: either 300 mg of nilotinib twice daily (n = 282), 400 mg of nilotinib twice daily (n = 281), or 400 mg of imatinib once daily (n = 283). With nilotinib, there was a 5-10 year increase in MMR, MR4, and MR4.5 cumulative rates compared to imatinib. Response rates with nilotinib were higher than with imatinib at both five and 10 years in the combined analysis of the two nilotinib arms.

In addition, Ibrahim *et al.,*[16] who conducted a pilot study on whether or not patients who have just been diagnosed with CML-C, or chronic phase CML, can safely and effectively proceed from nilotinib to imatinib, found that the switch was safe and effective. 75% of patients obtained MMR at 12 months, with 44% achieving MR4.5 on nilotinib treatment.

We found that no Nilotinib individuals experienced a skin rash, whereas G1, G2, and G3 rashes appeared, correspondingly, in the Imatinib group of patients11 (24%), 4 (9%) and 6 (13%) respectively, distinctly differentiating the two categories (P0.001). The Imatinib group experienced significantly more nausea than the Nilotinib group (P = 0.002). 20 (44%) and 8 (16%) of the Imatinib-treated patients developed G1 and G2 nausea, Yet, just 15 (32%) of the Nilotinib-treated patients experienced G1 nausea.It was statistically significant (p = 0.002). In the Imatinib group, G1 and G2 fatigue were significantly more common (P = 0.001), occurring in 28 (61%) and 3 (6%) patients, respectively. While only 10 (22%) and 6 (12%) patients in the Nilotinib group experienced G1 or G2 Fatigue. In contrast, Nilotinib patients were more likely to experience diarrhea, with 32% of patients experiencing G1 diarrhea and 12% experiencing G2 diarrhea, compared to 28% of Imatinib patients. The rate of diarrhea was significantly different between the two groups (P = 0.031).

Our study showed that at 6 months : mean EF ± SD shows significant difference in EF results after treatment between two arms with P value 0.02%, 12 months : mean EF± SD shows significant difference in EF results after treatment between two arms with P value 0.0001%

Kantarjian *et al.,*[15] revealed that electrocardiogram when comparing nilotinib with imatinib, Overall, nilotinib was associated with a higher incidence of QT prolongation (6.8% at 300 mg bid; 7.9% at 400 mg bid); rates of any-grade and grade 3/4 AE groups were similar.

Our results showed that compared to the Imatinib group, those who took Nilotinib had a far higher rate of survival (median survival was 30 months versus a total of 25 months for the Nilotinib group and Imatinib group, respectively; P = 0.01). It shows significant difference in PFS at 5 years results after treatment between two arms with P value 0.0001, It shows significant difference in 5 years survival rate results after treatment between two arms with P value 0.011.

Also, Aly *et al.,*[17] Patients who took Nilotinib had a progression-free time that was 23.44 months on average (97.6%), while patients who took placebo had a progression-free period that was 19.2 months on average (80%) (P = 0.01). Nilotinib patients had a significantly higher rate of survival than those given imatinib (median survival, 30 months vs. 25 months for the nilotinib and imatinib groups, respectively; P = 0.01).

This is consistent with Wang *et al.,* [18] who found that median survival in the nilotinib arm was 22.3 months and in the imatinib arm it was 22.6 months.

Also, Kantarjian *et al.*[19] In subgroups of younger patients, the nilotinib arms showed statistically and clinically significant improvements over the imatinib arm for freedom from progression to AP/BP, overall survival, and progression-free survival at 10 years. Age-specific 10-year OS and PFS rates were significantly lower (indicating poorer survival) in older patient subsets compared to overall rates or rates in younger patients (especially in both nilotinib arms compared with imatinib), though these results should be interpreted with caution due to the small sample size in the older subset.

Our research has a few limitations. First, is limited patient population and it's a single-center design. We did not evaluate the effect of both treatments on fluid retention and cardiovascular side effects. Unfortunately, we were unable to calculate the aggregate survival rate because none of our patients passed away**.**

Conclusion

Patients with chronic myeloid leukemia (CML) who had an unsatisfactory response to prior treatment responded to both Nilotinib and high-dose Imatinib, however the latter was associated with a more immediate and substantial molecular response, better survival outcomes, and fewer side effects. Nilotinib, 300 milligrams twice daily, is recommended based on positive effectiveness and safety data as a first-line treatment for optimal outcomes. The benefit-risk profile should be thoroughly evaluated in the context of individual treatment objectives.

REFERENCES

1. S. Soverini, M. Mancini, L. Bavaro, M. Cavo, and G. Martinelli, "Chronic myeloid leukemia: the paradigm of targeted therapy", ***J Hematol Oncol***, 13(1), 2 (2020).
2. E. Jabbour, and H. Kantarjian, "Chronic myeloid leukemia: 2020 update on diagnosis, therapy, and monitoring", ***Am J Hematol***, 95(6), 691–709 (2020).
3. A. Hochhaus, R.A. Larson, F. Guilhot, J.P. Radich, S. Branford, T.P. Hughes, and H.M. Kantarjian, "Long-term outcomes of imatinib treatment for chronic myeloid leukemia", ***N Engl J Med***, 376(10), 917-927 (2020).
4. M. Baccarani, M.W. Deininger, G. Rosti, and A. Hochhaus, "European LeukemiaNet recommendations for the management and therapy of chronic myeloid leukemia: 2020 update", ***Leukemia***, 34(4), 966–984 (2020).
5. T.P. Hughes, M.J. Mauro, and J.E. Cortes, "Deep molecular responses in CML: The new goal of therapy?", ***Clin Cancer Res***, 25(3), 716–722 (2019).
6. J.P. Radich, and M. Deininger, "Chronic myeloid leukemia: Current treatment and future perspectives", ***Blood***, 132(4), 393–402 (2018).
7. G. Saglio, D.W. Kim, S. Issaragrisil, P. Le Coutre, G. Etienne, C. Lobo, and A. Hochhaus, "Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia", ***N Engl J Med***, 362(24), 2251-2259 (2010).
8. R.A. Larson, and A. Hochhaus, "Chronic myeloid leukemia in 2019: Moving towards cure", ***Hematol Oncol Clin North Am***, 33(3), 455-473 (2019).
9. A. Hochhaus, R.A. Larson, F. Guilhot, J.P. Radich, S. Branford, T.P. Hughes, and H.M. Kantarjian, "Long-term outcomes of imatinib treatment for chronic myeloid leukemia", ***N Engl J Med***, 376(10), 917-927 (2020).
10. A. Hochhaus, G. Saglio, R.A. Larson, D.W. Kim, G. Etienne, G. Rosti, *et al.*, "Nilotinib is associated with a reduced incidence of BCR-ABL mutations vs imatinib in patients with newly diagnosed chronic myeloid leukemia in chronic phase", ***Blood***, 121(18), 3703-3708 (2013).
11. T. Masszi, F.J. Giles, J.P. Radich, D.M. Ross, M.T. Gomez Casares, *et al.*, "Treatment-free remission following frontline nilotinib in patients with chronic myeloid leukemia in chronic phase: results from the ENESTfreedom study", ***Leukemia***, 31(7), 1525-1531 (2017).
12. D.M. Ross, T. Masszi, M.T. Gómez Casares, A. Hellmann, J. Stentoft, E. Conneally, *et al.*, "Durable treatment-free remission in patients with chronic myeloid leukemia in chronic phase following frontline nilotinib: 96-week update of the ENESTfreedom study", ***J Cancer Res Clin Oncol***, 144(5), 945-954 (2018).
13. J.P. Radich, A. Hochhaus, T. Masszi, A. Hellmann, J. Stentoft, M.T. Casares, *et al.*, "Treatment-free remission following frontline nilotinib in patients with chronic phase chronic myeloid leukemia: 5-year update of the ENESTfreedom trial", ***Leukemia***, 35(5), 1344-1355 (2021).
14. R.E. Clark, F. Polydoros, J.F. Apperley, D. Milojkovic, C. Pocock,

G. Smith, *et al.*, "De-escalation of tyrosine kinase inhibitor dose in patients with chronic myeloid leukaemia with stable major molecular response (DESTINY): an interim analysis of a non-randomised, phase 2 trial", ***Lancet Haematol***, 4(7), e310-316 (2017).

15. H.M. Kantarjian, A. Hochhaus, G. Saglio, C. De Souza, I.W. Flinn, L. Stenke, *et al.*, "Nilotinib versus imatinib for the treatment of patients with newly diagnosed chronic phase, Philadelphia chromosome-positive, chronic myeloid leukaemia: 24-month minimum follow-up of the phase 3 randomised ENESTnd trial", ***Lancet Oncol***, 12(9), 841-851 (2011).
16. A. Ibrahim, N. Moukalled, R. Mahfouz, J. El Cheikh, A. Bazarbachi, I. Abou Dalle, "Safety and Efficacy of Elective Switch from Nilotinib to Imatinib in Newly Diagnosed Chronic Phase Chronic Myeloid Leukemia", ***Clin Hematol Int***, 4(1-2), 30-34 (2022).
17. A.H. Aly, A.E. Khalifa, E.A. Gadallah, "Efficacy of Nilotinib versus Imatinib in Philadelphia Positive Patients with Chronic Myeloid Leukemia in Early Chronic Phase Who Have a Warning Molecular Response to Imatinib", ***J Cancer Ther***, 9(11), 883 (2018).
18. J. Wang, Z.X. Shen, G. Saglio, J. Jin, H. Huang, Y. Hu, *et al.*, "Phase 3 study of nilotinib vs imatinib in Chinese patients with newly diagnosed chronic myeloid leukemia in chronic phase: ENESTchina", ***Blood***, 125(18), 2771-2778 (2015).
19. H.M. Kantarjian, T.P. Hughes, R.A. Larson, D.W. Kim, S. Issaragrisil, P. Le Coutre, *et al.*, "Long-term outcomes with frontline nilotinib versus imatinib in newly diagnosed chronic myeloid leukemia in chronic phase: ENESTnd 10-year analysis", ***Leukemia***, 35(2), 440-453 (2021).

Bull. Pharm. Sci., Assiut University, Vol. 47, Issue 2, 2024, pp.1177-1188.

نشرة العلوم الصيدلية
جامعة أسيوط
BULL. PHARM. SCI. Assiut Univ.

مقابل الإيماتينيب في المرضى الذين يعانون من سرطان الدم النخاعي المزمن المشخص حديثًا – المرحلة المزمنة

آيات مرسي محمد[1*] – هدى حسن عيسى[1] – عبير فايق أمين[1] – جان جورج ماكسويل[2] – دعاء علي جمال[1]

[1]قسم علاج الأورام – كلية الطب – جامعة أسيوط

[2]مستشفي سوهاج للتأمين الصحي، مصر

المقدمة: سرطان الدم النخاعي المزمن هو سرطان الدم التدريجي. تعتبر مثبطات التيروزين كيناز النيلوتينيب والإيماتينيب علاجات فعالة للمرضى الذين تم تشخيصهم حديثًا بسرطان الدم النخاعي المزمن.

الهدف: أحد أهداف هذا البحث هو مقارنة فعالية النيلوتينيب والإيماتينيب في علاج الحالات المشخصة حديثًا لسرطان الدم النخاعي المزمن من حيث الهجوع الدموي والخلوي والجزيئي.

طرق الدراسة: شملت هذه الدراسة ٩٢ حالة تم تشخيصها حديثاً بسرطان الدم النخاعي المزمن ؛ شملت المجموعة (I) المرضى الذين عولجوا بـ الإيماتينيب ٤٠٠ مجم مرة واحدة يوميًا بينما ضمت المجموعة (II)المرضى الذين عولجوا بـ والنيلوتينيب ٣٠٠ مجم مرتين يوميا. تم تقييم المرضى بشكل شامل كل ثلاثة أشهر على مدار ثلاث سنوات، بما في ذلك التاريخ الدقيق والفحوصات البدنية والمخبرية. تم تقييم الاستجابات الجزيئية كل ٣ أشهر بواسطة RQ-PCR لمدة ٣ سنوات. تم تقدير نظام التشغيل والتحرر من التقدم إلى AP/BC كل ٣ أشهر لمدة ٣ سنوات.

النتائج: تم تسجيل اثنين وتسعين مشاركا بعد تشخيص إصابتهم بسرطان الدم النخاعي المزمن لأول مرة. خلال فترة متابعة الدراسة التي استمرت ثلاث سنوات، شارك ٤٦ شخصًا في مجموعة النيلوتينيب وشارك ٤٦ شخصًا في مجموعة الإيماتينيب. لم تكن هناك خسائر أو وفيات للمرضى خلال فترة التجربة. من حيث الآثار الجانبية الدموية، تم تعريف فقر الدم على أنه مستوى الهيموجلوبين أقل من ١٠ ملجم٪. كان ستة مرضى في مجموعة النيلوتينيب ١٣%، مقارنة بـ ١٠ أفراد في مجموعة الإيماتينيب ٢٢%، يعانون من فقر الدم .ثلاثة (١٣٪ من المجموع) من المرضى في كل مجموعة عانوا من نقص الكريات البيض (إجمالي عدد الكريات ٣)؛ .لم يظهر الأفراد الذين عولجوا بالنيلوتينيب أي حالات نقص الصفائح الدموية، في حين أن ٤ (٨٪) من المرضى الذين عولجوا بالإماتينيب كان لديهم نقص في معدل الصفائح الدمويه. تباينت معدلات البقاء على قيد الحياة بدون تقدم لمدة خمس سنوات

بعد العلاج بشكل كبير بين المجموعتين . بعد العلاج، كان للذراعين معدلات بقاء مختلفة لمدة ٥ سنوات.

الاستنتاج: المرضى الذين يعانون من سرطان الدم النخاعي المزمن والذين تم إعطاؤهم إما نيلوتينيب أو إيماتينيب بجرعة عالية شهدوا استجابة، ولكن كان لدى نيلوتينيب استجابة جزيئية أكثر فورية وعميقة، وتحسنت فرص البقاء على قيد الحياة، وآثار ضارة أقل. يوصى باستخدام النيلوتينيب ٣٠٠ مجم مرتين يوميا كعلاج الخط الأول نظرًا لفعاليته وسلامته.