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Nilotinib and Dasatinib As Second-line Therapy For Chronic Myeloid Leukemia Patients: Effectiveness And Tolerance Profile In Western Algeria

Assia Ghezali [1,2*], Amel Sebaa [1,2], Imene Ghezali [3], Cherifa Akkal [4], Salaheddine Elherrag[1,2], Nadjia Fertout-Mouri[5], Sofiane Bouazza[2]

1-Department of Biology, Faculty of Life and Natural Sciences, Djillali Liabes University, Sidi Bel Abbes, Algeria.
2-Laboratory of Molecular Microbiology, Proteomics and Health, Djillali Liabes University, Sidi Bel Abbes, Algeria.
3- Galenic pharmacy laboratory Faculty of Pharmacy of Algiers, Algeria.
4- EPH Mascara hematology department, Mascara, Algeria.
5- Laboratory of Plant Biodiversity: Conservation and Valorization, Faculty of Nature and Life Sciences, Djillali Liabes University of Sidi Bel
Abbes, Algeria
Corresponding author *e-mail : ghazalia18bio@gmail.com
Tel : 0782073640
Email addresses:

AS: sebaamel@yahoo.fr tel: +213 (0)551332958
IG: ghezali89@gmail.com tel: +213 (0)782073640
CA: hamdi18@hotmail.fr tel +213 (0) 552924563
SE: Salaheddine.elherrag@gmail.com tel +213 (0) 658399448
NFM: nadjiafertout@yahoo.fr tel +213 (0) 557174042
SB: sofiane.bouazza@outlook.com tel +213 (0) 0770148824

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Abstract

Purpose: The prognosis of patients with chronic myeloid leukemia (CML) has significantly improved with the introduction of Imatinib. However, approximately 30% of patients develop resistance or intolerance. This study aims to evaluate the molecular response to second-generation tyrosine kinase inhibitors (TKIs) and explore patient characteristics and treatment strategies in western Algeria.

Materials and Methods: This retrospective analysis includes 422 CML patients treated over an 11-year period across seven hematology departments in western Algeria.

Results: 422 patients received Imatinib as first-line therapy, however 45.3% experienced intolerance, and 54.7% developed resistance, leading 137 patients (32.46%) to switch to second line treatment. In this group of 137 patients, Major molecular response (MMR) was obtained in 22% of Dasatinib-treated patients, 11.4% attained a Deep Molecular Response (DMR), and one patient achieved a Completed Molecular Response (CMR). In contrast, 36% of patients receiving Nilotinib achieved MMR, 27.8% attained a DMR, and two patients reached CMR.

A comparative analysis of mortality rates revealed a significantly higher incidence in the Dasatinib cohort (26%) compared to the Nilotinib cohort (4.9%) (p=0.002).

Conclusion: Our findings indicate that Nilotinib demonstrates superior efficacy over Dasatinib in achieving higher molecular response rates, mitigating disease progression, and reducing mortality among CML patients in western Algeria.

Keywords: Chronic myeloid leukemia, Dasatinib, Nilotinib, Tyrosine kinase inhibitor, Second line therapy.

1. Background

Chronic Myeloid Leukemia (CML) is categorized as a myeloproliferative disorder, with a relatively low incidence rate estimated at around 1 to 2 cases /100,000 adults [1]. In Algeria, the reported incidence of CML in 2014 stood at 0,53 cases per 100,000 inhabitants, resulting in a total of 1030 cases. [2]. The Philadelphia chromosome (Ph), which results from a reciprocal translocation between chromosome 9 and 22, is a characteristic of CML, denoted as t(9;22), leading to the formation of the fusion gene *BCR-ABL1* [3]. The persistently active BCR-ABL1 tyrosine kinase triggers a highly intricate signaling transduction pathway, resulting in a strong resistance to chemotherapy [4].

The introduction of BCR-ABL1-targeting tyrosine kinase inhibitors (TKIs) revolutionized CML management, ushering in a new era in oncology. With the approval of three successive generations of TKIs, a significant percentage of CML patients now achieve prolonged remissions and near-normal life expectancy.

Despite the promising long-term outcomes achieved with Imatinib in the management of patients diagnosed with CML, it is noteworthy that approximately 30% of patients will ultimately require alternative treatment options. Amongst this patients cohort, two potent 2GTKIs have demonstrated efficacy: namely, Nilotinib and Dasatinib [7]. As indicated in the guidelines of the NCCN (National Comprehensive Cancer Network) and recommendations from the European Leukemia Net (ELN), clinical investigations involving 2G TKIs have consistently reported markedly profound and more rapid treatment responses [6].

In two phase II clinical trials of chronic-phase CML patients resistant or intolerant to Imatinib, approximately 50% achieved a CCyR with second-line Dasatinib or Nilotinib[8], the application of Nilotinib, Dasatinib, and Bosutinib as second line treatments has demonstrated effectiveness in attaining Major Molecular Response (MMR).

Attaining a profonde molecular response in patients with CML, defined as MR4.5 (BCR-ABL1 $\leq$ 0.0032% on the international scale) or MR4 (BCR-ABL1 $\leq$ 0.01% on the international scale), is crucial. This response is linked to improved overall survival and progression-free survival rates [10].

In Algeria, the introduction of ‘Imatib’ (manufactured by CIPLA-India) occurred in 2006. However, a subset of patients did not achieve optimal responses with first-line therapy or

experienced adverse effects. These patients were offered second-line treatment options, including TKIs such as Dasatinib and Nilotinib.

Up to the present time, there is a lack of published studies conducted in Algeria that directly compare the response and outcomes of Dasatinib and Nilotinib as second-line treatments within a cohort of CML patients who demonstrate resistance/intolerance to Imatib from CIPLA-India. The primary objective of our study was to evaluate molecular responses, provide insights into patient's characteristics, and describe treatment strategies employed among CML patients hailing from the northwestern region of Algeria.

2. Methods

We carried out a retrospective analysis of 422 consecutive patients diagnosed with CML, who were under the care of seven hematological departments in western Algeria over an 11-year period, spanning from January 2007 to December 2017. Patient data were gathered from electronic medical records during their clinic visits. The assessment of molecular markers was conducted at various time intervals using real-time quantitative PCR, specifically employing the Applied Biosystems 7500 Real-Time PCR system [11], as per the guidelines provided by European Leukemia Net (ELN) [12]. Patients who began treatment with either Nilotinib or Dasatinib as their second line therapy were categorized into the respective dasatinib or Nilotinib cohorts.

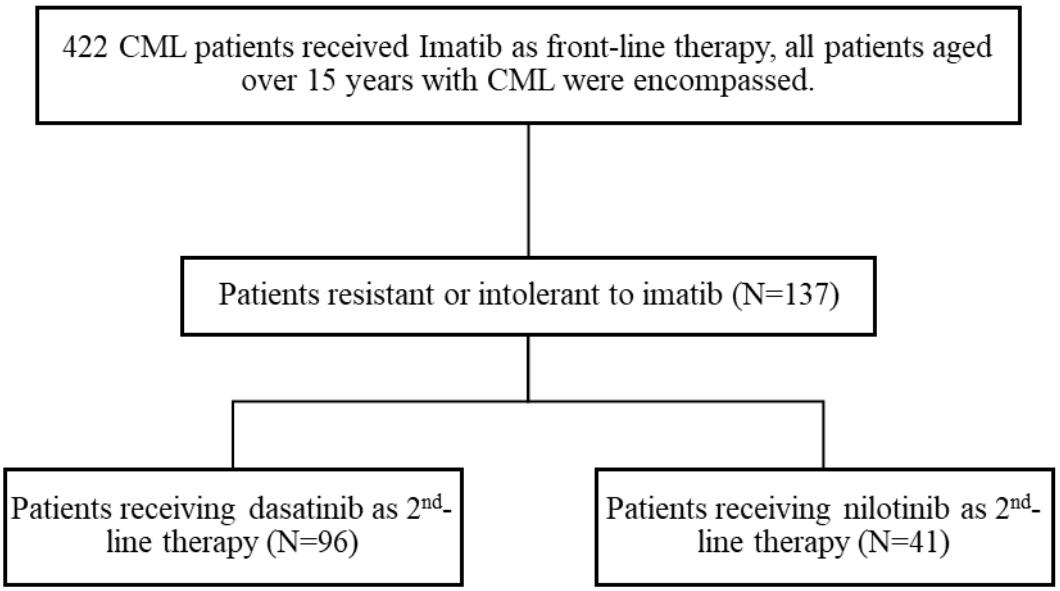
Statistical analysis

We performed all statistical analyses using the statistical programming environment R (R Core Team, 2023) [13], and table generation was accomplished with utilization of the gtsummary package [14].

Standard deviations, ranges, means, and medians were used to characterize numerical variables, whereas frequencies and percentages were used to characterized categorical variables. To compare continuous distributions between two paired groups, the Wilcoxon rank sum test was employed. Moreover, we utilized Pearson's Chi-squared test, particularly when dealing with limited sample sizes, Fisher's exact test, to assess the presence of significant associations between two categories. For predicting the probability of binary outcome and figuring out odds ratios (ORs) with their respective 95% confidence intervals (CIs), we employed a logistic regression model using maximum likelihood estimation. We computed

the Cox proportional hazard ratio (HR) and its associated 95% confidence interval (CI) to assess overall survival subsequent to treatment with Nilotinib or Dasatinib.

2.1. Study design



3. Results

3.1. Baseline characteristics of patients and outcomes associated with the employment of second generation TKIs

There were 422 patients overall between January 2007 and December 2017, receiving Imatib as their initial treatment. However, due to either intolerance (45.3%) or resistance (54.7%) to Imatinib, 137 patients (32.46%) necessitated a switch to a second line of tyrosine kinase inhibitors of the second generation (2GTKIs). Out of the 137 patients who were administered second line therapy, 41 (29.9%) were treated with Nilotinib, while 96 (70.1%) received Dasatinib. Table 1 provides a summary of the baseline demographic, clinical, and treatment characteristics. The median age of patients within the Nilotinib group was 36 years (Mean ± SD 39 ± 13), and in the Dasatinib group, it was 48 years (Mean ± SD 46 ± 13). The sex ratio was 0.95 in the Nilotinib cohort and 0.88 in the Dasatinib cohort. Notably, females were the predominant gender in both treatment groups.

Table 1: Patients' characteristics according to sex

Characteristic	N	Overall N = 137[1]	Female N = 72[1]	Male N = 65[1]	p-value[2]
Age	137				0.3
Mean ± SD		44 ± 13	45 ± 13	43 ± 14	
Median		44	46	44	
Range		17, 80	17, 80	18, 67	
CML phase	137				0.053
Accelerated		15 (11%)	4 (5.6%)	11 (17%)	
Blastic Phase		1 (0.7%)	1 (1.4%)	0 (0%)	
Chronic		121 (88%)	67 (93%)	54 (83%)	
Sokal score	137				**<0.001**
High-risk		53 (39%)	17 (24%)	36 (55%)	
Intermediate		59 (43%)	38 (53%)	21 (32%)	
Low-risk		25 (18%)	17 (24%)	8 (12%)	
Eutos score	137				0.2
High-risk		28 (20%)	12 (17%)	16 (25%)	
Low-risk		109 (80%)	60 (83%)	49 (75%)	
Death	137				0.5
Lost to follow-up		3 (2.2%)	2 (2.8%)	1 (1.5%)	
NO		107 (78%)	58 (81%)	49 (75%)	
YES		27 (20%)	12 (17%)	15 (23%)	

[1]n (%)
[2]Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

3.2. Patient characteristics

Regarding the prior Imatib therapy received before the switch to second-line treatment, noteworthy differences were noted between the Dasatinib and Nilotinib groups. In the Nilotinib cohort, a large percentage of patients transitioned to an alternative treatment regimen due to secondary resistance to Imatinib (61%) compared to the dasatinib cohort (52.1%). Conversely, in the Nilotinib group, a reduced patient population made a switch due to intolerance to (39%) in contrast to the dasatinib group, where 48% of patients switched for this reason.

A greater percentage of patients within the Dasatinib cohort (21%) exhibited a low Sokal risk stratification at the time of their CML diagnosis, compared to the Nilotinib group (12%). Nevertheless, these differences did not reach statistical significance (p=0.4). Sokal risk stratification revealed that 39% of the entire cohort had a high risk, 43% possessed an intermediate-risk profile, while 18% exhibited a low risk profile (Table 2). In terms of patient gender, males are stratified into the high-risk category (55% vs. 24% for females p<0.001), while females are categorized within the intermediate-risk group. This same pattern was

observed when considering the EUTOS score, where males were assigned to the high-risk classification, while females were placed in the low-risk category. This trend holds true for both types of treatment under consideration (Figure 2).

Table 2: Patients' characteristics according to 2nd Gen TKI

Characteristic	N	Overall N = 137[1]	Dasatinib 100-140 mg N = 96[1]	Nilotinib 800 mg N = 41[1]	p-value[2]
Age	137				**0.002**
Mean ± SD		44 ± 13	46 ± 13	39 ± 13	
Median		44	48	36	
Range		17- 80	17- 80	19- 66	
Sexe	137				0.8
Female		72 (53%)	51 (53%)	21 (51%)	
Male		65 (47%)	45 (47%)	20 (49%)	
CML phase	137				0.8
Accelerated		15 (11%)	10 (10%)	5 (12%)	
Blastic Phase		1 (0.7%)	1 (1.0%)	0 (0%)	
Chronic		121 (88%)	85 (89%)	36 (88%)	
Sokal score	137				0.4
High-risk		53 (39%)	37 (39%)	16 (39%)	
Intermediate		59 (43%)	39 (41%)	20 (49%)	
Low-risk		25 (18%)	20 (21%)	5 (12%)	
Eutos score	137				0.5
High-risk		28 (20%)	21 (22%)	7 (17%)	
Low-risk		109 (80%)	75 (78%)	34 (83%)	
Death	137				**0.002**
Lost to follow-up		3 (2.2%)	1 (1.0%)	2 (4.9%)	
NO		107 (78%)	70 (73%)	37 (90%)	
YES		27 (20%)	25 (26%)	2 (4.9%)	
OS YEARS	134				0.3
Mean ± SD		4.41 ± 2.34	4.27 ± 2.32	4.73 ± 2.38	
Median		4.00	4.00	4.00	
Range		1.00- 10.00	1.00-10.00	1.00- 9.00	
2nd line treatment duration	134				0.3
Mean ± SD		4.41 ± 2.34	4.27 ± 2.32	4.73 ± 2.38	
Median		4.00	4.00	4.00	
Range		1.00- 10.00	1.00- 10.00	1.00- 9.00	
Imatinib Intolerance or Resistance	137				0.3
Intolerance		62 (45%)	46 (48%)	16 (39%)	
Resistance		75 (55%)	50 (52%)	25 (61%)	
2nd line treatment response to 2nd Gen TKI	115				**0.049**
Intolerance		17 (15%)	14 (18%)	3 (8.3%)	
MMR		30 (26%)	17 (22%)	13 (36%)	
MR4		2 (1.7%)	1 (1.3%)	1 (2.8%)	
MR4,5		7 (6.1%)	3 (3.8%)	4 (11%)	
MR5		10 (8.7%)	5 (6.3%)	5 (14%)	
CMR		3 (2.6%)	1 (1.3%)	2 (5.6%)	
Resistance		42 (37%)	34 (43%)	8 (22%)	
Treatment Refusal		2 (1.7%)	2 (2.5%)	0 (0%)	
Warning		2 (1.7%)	2 (2.5%)	0 (0%)	
3rd line treatment response to 2nd Gen TKI	29				0.4
intolerance		2 (6.9%)	2 (7.7%)	0 (0%)	

MMR		5 (17%)	4 (15%)	1 (33%)	
MR4		2 (6.9%)	1 (3.8%)	1 (33%)	
MR5		2 (6.9%)	2 (7.7%)	0 (0%)	
resistance		17 (59%)	16 (62%)	1 (33%)	
shortage		1 (3.4%)	1 (3.8%)	0 (0%)	
3rd line TKI	37				**<0.001**
DASA 100-140 mg		4 (11%)	0 (0%)	4 (100%)	
Nilo 800 mg		33 (89%)	33 (100%)	0 (0%)	
Monitoring duration 2nd line	49				0.13
Mean ± SD		13 ± 12	11 ± 10	18 ± 16	
Median		10	8	18	
Range		1- 60	1- 48	3-60	

[1]n (%)
[2]Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

3.3. Molecular response and outcome

six months after initiating the second line therapy, a total of 96 patients receiving Dasatinib (22%) achieved a MMR, while 4 of them (11,4%) attained a deeper molecular response (DMR), characterized as MR^4, $MR^{4,5}$ and MR^5 and one patient achieved CMR. However, 34 patients (43%) were resistant and 14 (18%) were intolerant (table 2).

In the Nilotinib cohort, after a minimum of 6 months following the initiation of second line therapy, 13 out pf 41 patients (36%) attained a MMR, 10 (27,8%) achieved a DMR, and two patients reached a CMR. Nevertheless, 8 patients (22%) exhibited resistance, and 3 (8,3%) experienced intolerance to the treatment. The disparities between the two cohorts were demonstrated statistically meaningful (p=0,049) (Figure 3).

When assessing the attainment of the most favorable molecular response, the nilotinib group had the best outcome compared to Dasatinib, otherwise, we recorded the lowest percentages of patients resistant, and intolerant compared to the Dasatinib cohort. No significant differences were detected among males and females in the two groups (P=0,9) (Table 2).

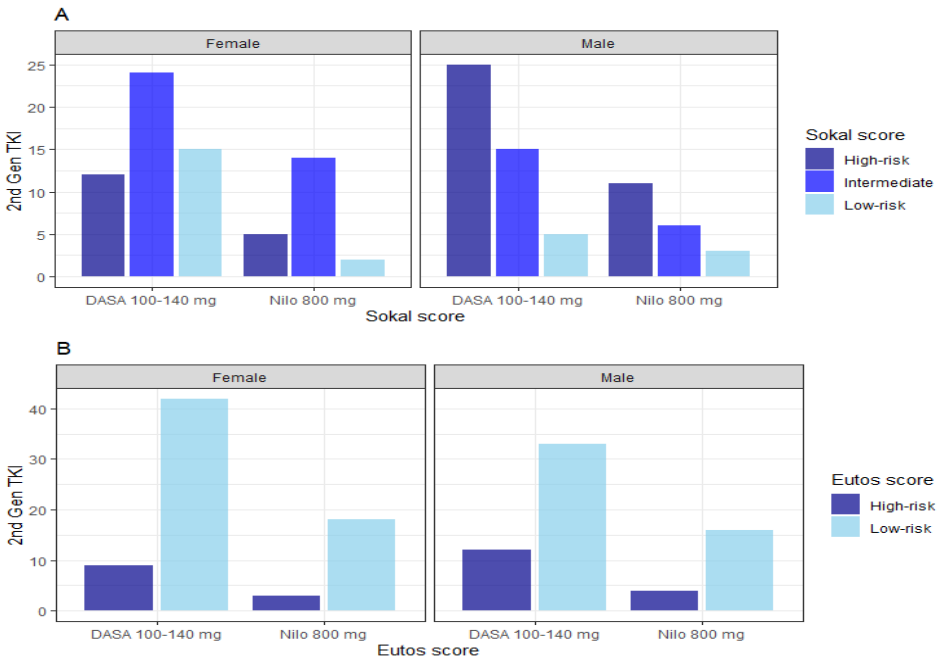


Figure 1: *frequency patients receiving 2nd Gen TKI according to disease scores and sex. A) according to Sokal score. B) according to Eutos score.*
2nd Gen TKI: Second Generation Tyrosine Kinase Inhibitors, Dasa: Dasatinib, Nilo: Nilotinib.

3.4. Progression, and overall survival

The median duration of post-treatment monitoring for patients in the Nilotinib cohort was 18 (ranging from 3 to 60 months), whereas for those in the Dasatinib cohort, it was 8 months (ranging from 1 to 48 months).

In the Nilotinib cohort, 4.9% of patients experienced disease progression, while in the Dasatinib cohort, a higher proportion, 10.4%, demonstrated disease progression.

Regarding overall survival, patients administered Nilotinib exhibited a hazard ratio (HR) of 0,84, 95% CI (0.58-1.21), p = 0.31 in contrast to those receiving Dasatinib treatment indicating that the Nilotinib group has a slightly higher overall survival time compared to the Dasatinib group; nevertheless, it is noteworthy that these distinctions did not attain statistical significance (Figure 4). Otherwise, we noted a significantly disparity in mortality rates between the two groups, favoring the Dasatinib cohort, with a mortality rate of 26%, as opposed to the Nilotinib cohort, which had a notably lower rate of 4.9% (p=0.002). 73% of patients in the Dasatinib group were still alive at the time of assessment, compared to 90% of patients in the Nilotinib group.

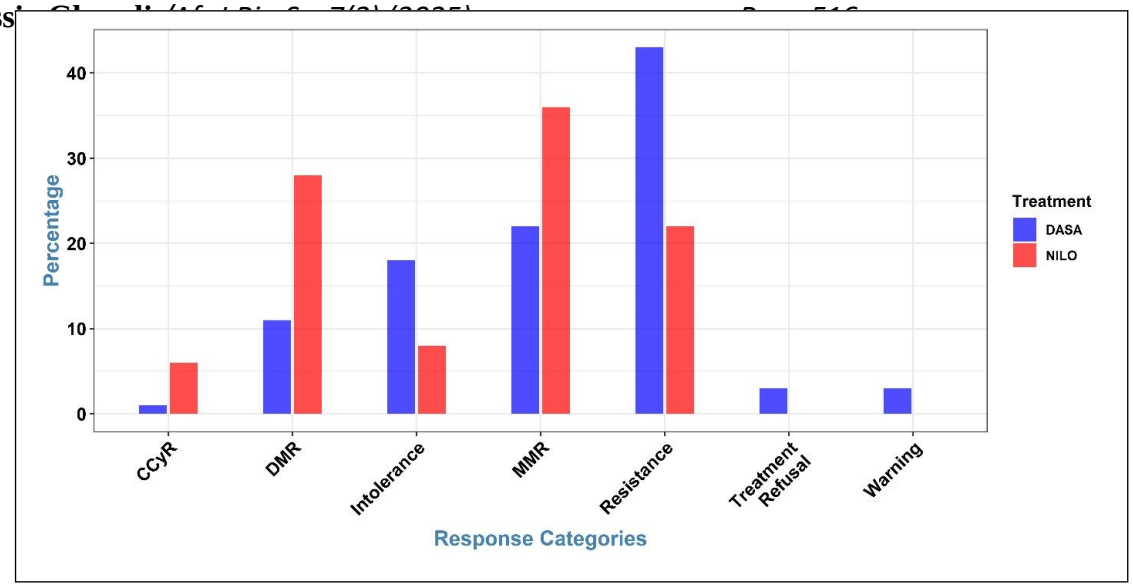


Figure 2: Treatment response of patients receiving treatment with 2nd Gen TK.

3.4. The use of 2GTKIs Nilotinib and Dasatinib as a third line treatment option

A double switch was observed in 27% of patients in our analysis, Nilotinib was prescribed to 33 patients following the failure of Imatinib/Dasatinib, and 4 patients received Dasatinib after experiencing treatment failure with Nilotinib.

With regard to the attainment of the optimal molecular response, the Nilotinib group exhibited superior outcomes when compared to the Dasatinib group, and these disparities were statistically significant (0,001). 51,4% had an intermediate Sokal risk score, 35,1% presented a high-risk score, while only 13,5% had a low-risk score.

Three patients did not respond to the three TKIs first, second, and third-line treatment. 26 (70,3%) of our patients were alive whereas 11 (29,7%) died.

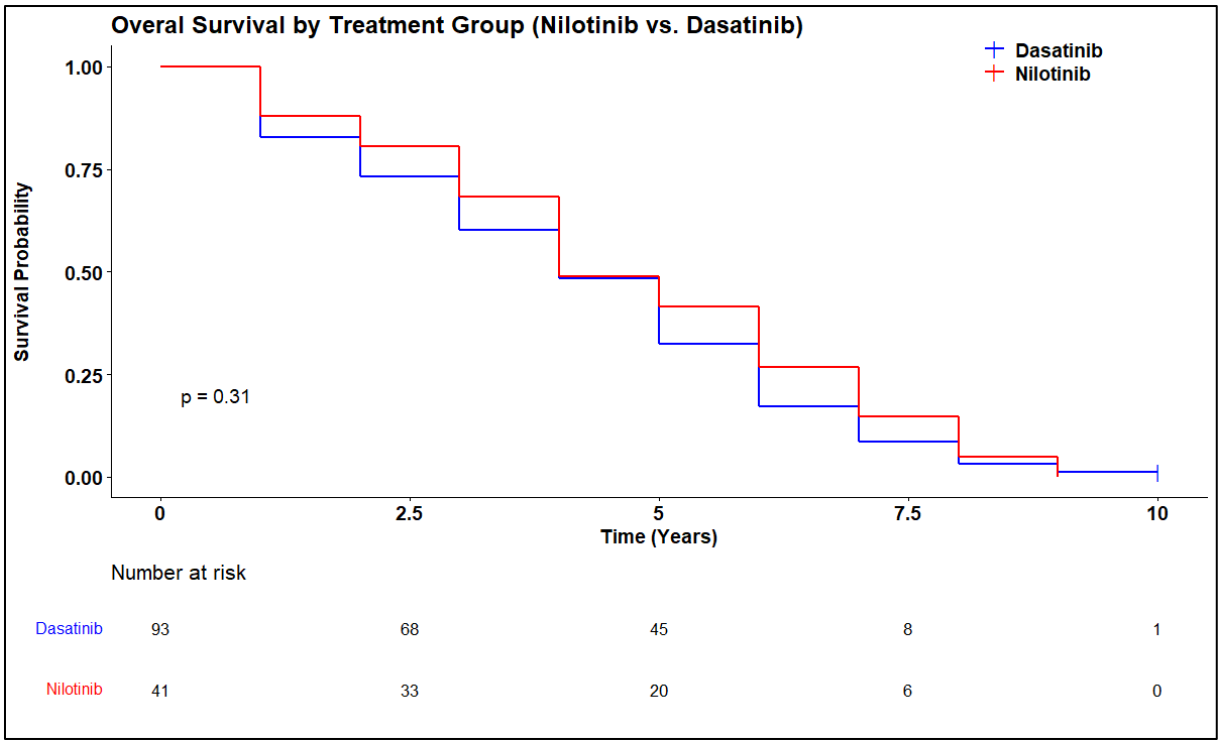


Figure 4: Overall survival of patients treated with 2nd generation TKI (Dasatinib or Nilotinib)

4. Discussion

We report the findings of our retrospective analysis, which included 137 consecutive patients suffering from CML in the western region of Algeria. These patients transitioned to second line treatment with either Nilotinib or Dasatinib.

The primary objective of the current study was to evaluate the clinical outcomes associated with second line treatment in patients diagnosed with CML.

Our findings indicate that, when compared to patients receiving Dasatinib, those who were administered Nilotinib demonstrated a significantly elevated rate of attaining deeper molecular responses, precisely referred to as MR^4, $MR^{4,5}$ and MR^5.

Our study's results align with previous research, reinforcing the notion that patients receiving Nilotinib tend to achieve better treatment responses than those treated with Dasatinib [15]. Our findings were entirely consistent with the investigation conducted by Jorge Cortes et al. [16]. Additionally, Scalzulli et al. [17] reported no significant outcome differences based on the specific second generation TKIs utilized , with a noted Major Molecular Response (MMR) incidence in 70% of cases. Similarly, Shah et al. [18] observed a Major Molecular Response (MMR) incidence of 46% after 7 years in a cohort of 670 patients, further supporting the effectiveness of 2G TKIs in the management of CML.

Upon switching to secondary phase of treatment, patients within the Nilotinib division exhibited a decreased risk of disease progression in contrast to those in the Dasatinib cohort. Notably, this observation aligns perfectly with the investigation carried out by Griffin and colleagues , emphasizing the consistency of our findings with existing research [18]. Conversely, Scalzulli and colleagues did not detect notable disparities in treatment outcomes.

It is worth emphasizing that a restricted number of studies have investigated the outcomes related to achieving deep molecular responses in patients receiving second line treatment for CML. As far as our knowledge extends, this study represents the inaugural effort in Algeria to compare clinical outcomes among CML patients undergoing second line therapy with Nilotinib and those opting for Dasatinib. This novel research contributes valuable insights to the field of CML treatment in the Algerian context.

In the present analysis, a greater number of patients in the Nilotinib group made the switch due to the development of secondary resistance to Imatib. In the latest revision of the IRIS trial, it was observed that 15% of patients exhibited resistance to Imatinib, while 10% experienced intolerance to the treatment. based on statistical data from the literature regarding the transition to second generation treatments, it is commonly observed that patients who switch due to resistance typically face a less favorable prognosis compared to those who make the switch due to intolerance. No significant disparities were identified among patients who transitioned to second line therapy due to either intolerance or treatment ineffectiveness, according to our findings. In 321 patients treated with Nilotinib after being treated with imatinib Kantarjian and colleagues [10] documented the findings from the MD Anderson Cancer Center group. Among the resistant patients, 55% achieved CCyRs, while 63% of the intolerant patients attained CCyRs, with an average follow-up duration of 2,8 months.

The Sokal risk assessment demonstrated an elevated frequency of cytogenetic responses in patients with low or intermediate risk scores and extended event-free survival (EFS). These findings were consistent with observations from the IRIS trial and various real-word observations, including our smaller series, a greater percentage of patients in the Dasatinib group exhibited high Sokal risk scores. Another real-world investigation discovered that, when compared to Dasatinib, second line therapy with Nilotinib improved both life expectancy and the quality of life outcomes among patients with CML [20].

The Sokal risk stratification analysis in our study revealed that among the entire cohort, 39% of patients were categorized as high risk, 43% were placed in the intermediate risk category, and 18% were identified as having a low-risk profile. Interestingly, the findings from the study conducted by Scalzulli et al. [17] diverge significantly from our results. In their study,

merely 9% of the patients were categorized as high-risk category, while 40% fell into the intermediate-risk category, and 51% were classified as low-risk. These disparities in risk stratification between the two studies highlight potential differences in patient populations, treatment approaches, or other factors that may influence the distribution of risk categories among CML patients. Notably, when considering patient gender, a distinct pattern emerges. Specifically, a significant proportion of males were stratified into the high-risk category (55%), in stark contrast to females, where only 24% were classified as high-risk ($p<0.001$). Instead, females predominantly fell within the intermediate-risk group.

This gender-based risk stratification pattern remained consistent when applying the EUTOS score, further illustrating that males were consistently categorized as high-risk, while females consistently occupied the low-risk category. These findings emphasize the influence of gender on risk stratification in this context. Notably, Griffin et al. [19] and Scalzulli et al. [17] did not identify any significant differences related to gender when assessing the Sokal risk score and EUTOS score. These findings contrast with our own study's observations. These variations in results across studies underscore the complexity of factors that can impact risk assessment in CML patients and may be influenced by the specific characteristics of the study populations or methodologies employed. Further research may be required to better understand these discrepancies.

Cojbasic et al. [20] report that the age at the time of diagnosis can serve as a prognostic marker for predicting outcomes. Scalzulli et al [17] report that elderly patients, aged over 65 years, exhibited poorer survival rates (OS) and progression free survival (PFS). However, in our analysis, we did not identify a statistically significant different association between age and OS. Conversely, we observed a noteworthy dissimilarity in the mortality rate between the two groups favoring the Dasatinib cohort ($p=0,002$).

The analysis of overall survival (OS) in our investigation suggested that patients receiving Nilotinib had a hazard ratio (HR) of 0,84 accompanied by a 95% confidence interval (CI) spanning from 0,58 to 1,21 and p-value of 0,31 ($p=0,31$) when compared to those treated with Dasatinib. This suggests that the Nilotinib group exhibited a slightly higher OS time compared to the Dasatinib group, although these differences did not reach statistical significance. These findings align with previous research [19], where Nilotinib-treated patients also exhibited a reduced estimated hazard of mortality in comparison to those receiving Dasatinib. Nonetheless, this disparity did not reach statistical significance ($HR = 0.46$, $p = 0.067$).

Overall, in our investigation, approximately 27% of the patients transitioned to third line therapy with 2G TKIs as a result of resistance or intolerance. 33 patients in the Dasatinib cohort had to switch to Nilotinib as treatment of third line, four patients within the Nilotinib cohort had been switching to 3rd line Dasatinib, two patients underwent a bone marrow transplant and one patient switched on bosutinib as third-line treatment. In order to increase patient survival for those with a high SOKAL score, monitoring is essential for an effective therapeutic approach. 26 (70,3%) of our patients were alive whereas 11 (29,7%) died.

The present research was subject to several limitations due to its retrospective nature, reliance on medical records, and variations in data completeness and accuracy. These limitations included missing information in patient clinical reports, potential inaccuracies in the recording of medical background data by physicians, and a lack of uniformity in how patient information was documented across different hospitals. Additionally, in Algeria, molecular monitoring is not universally available to all patients, and mutational testing to refine treatment approaches was lacking. Consequently, the study was restricted to patients who had undergone at least one molecular monitoring in real-world clinical practice, further adding to the study's limitations.

5. Conclusions

Our findings strongly suggest that Dasatinib and Nilotinib are viable treatment choices amongst CML patients who have experienced Imatinib treatment failure. These second-generation TKIs are associated with increased rates of molecular response, reaffirming their effectiveness in CML management. Notably, compared to second-line Dasatinib treatment, Nilotinib therapy in the second line for patients experiencing CML may be correlated with a higher likelihood of attaining a DMR and a diminished risk of disease progression and low mortality rate. Further comprehensive studies are warranted to elucidate potential differences in the influence of different TKIs on the quality of life of and provide valuable insights for CML treatment decision-making in Algeria.

Conflicts of Interest The authors declare no conflicts of interests.

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Authors contributions Assia Ghezali authored the initial draft of the manuscript and integrated feedback from co-authors into subsequent iterations and acquisition of data. Imene Ghezali and Fertout-Mouri Nadjet contributed to structuring and study design of the manuscript. Akkal Cherifa participated to managing bibliographic references and analysis of data. Assia Ghezali, Salaheddine Elherrag, Sofiane Bouazza provided statistical analysis (selection of statistical tests, interpretation of results). All contributing authors participated in the critical review, offered substantive edits, and granted their approval for the ultimate iteration of the manuscript.

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References

[1] Jabbour, E., & Kantarjian, H. (2018). Chronic myeloid leukemia: 2018 update on diagnosis, therapy and monitoring. *American journal of hematology*, *93*(3), 442-459.

[2] Entasoltan, B., Bekadja, M. A., Touhami, H., Mehalhal, N., Zouaoui, Z., Mesli, N., ... & Michallet, M. (2017). Outcome of frontline treatment with "generic" imatinib in adult patients with chronic myeloid leukemia in Algerian population: a multicenter study. *Mediterranean journal of hematology and infectious diseases*, *9*(1).

[3] Faderl, S., Talpaz, M., Estrov, Z., O'Brien, S., Kurzrock, R., & Kantarjian, H. M. (1999). The biology of chronic myeloid leukemia. *New England Journal of Medicine*, *341*(3), 164-172.

[4] Amarante-Mendes, G. P., Rana, A., Datoguia, T. S., Hamerschlak, N., & Brumatti, G. (2022). BCR-ABL1 tyrosine kinase complex signaling transduction: challenges to overcome resistance in chronic myeloid leukemia. *Pharmaceutics*, *14*(1), 215.

[5] Osman, A. E., & Deininger, M. W. (2021). Chronic Myeloid Leukemia: Modern therapies, current challenges and future directions. *Blood reviews*, *49*, 100825.

[6] Jabbour, E., & Kantarjian, H. (2020). Chronic myeloid leukemia: 2020 update on diagnosis, therapy and monitoring. *American journal of hematology*, *95*(6), 691-709.

[7] Gora-Tybor, J., Medras, E., Calbecka, M., Kolkowska, A., Ponikowska-Szyba, E., Robak, T., & Jamroziak, K. (2013). Real-life comparison of severe vascular events and other non-hematological complications in CML patients treated with second line nilotinib or dasatinib. *Blood*, *122*(21), 1491.

[8] Giles, F. J., Le Coutre, P. D., Pinilla-Ibarz, J., Larson, R. A., Gattermann, N., Ottmann, O. G., ... & Kantarjian, H. M. (2013). Nilotinib in imatinib-resistant or imatinib-intolerant patients with chronic myeloid leukemia in chronic phase: 48-month follow-up results of a phase II study. *Leukemia*, *27*(1), 107-112.

[9] Shah, N. P., Guilhot, F., Cortes, J. E., Schiffer, C. A., Le Coutre, P., Brümmendorf, T. H., ... & Saglio, G. (2014). Long-term outcome with dasatinib after imatinib failure in chronic-phase chronic myeloid leukemia: follow-up of a phase 3 study. *Blood, The Journal of the American Society of Hematology*, *123*(15), 2317-2324.

[10] Kantarjian, H., & Cortes, J. E. (2014). Complete cytogenetic response, not deep molecular response, is associated with survival in chronic myeloid leukemia. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*, *32*(27), 3077-3077.

[11] Gabert, J., Beillard, E., Van der Velden, V. H. J., Bi, W., Grimwade, D., Pallisgaard, N., ... & Van Dongen, J. J. M. (2003). Standardization and quality control studies of 'real-time'quantitative reverse transcriptase polymerase chain reaction of fusion gene transcripts for residual disease detection in leukemia–a Europe Against Cancer program. *Leukemia*, *17*(12), 2318-2357.

[12] Baccarani, M., Deininger, M. W., Rosti, G., Hochhaus, A., Soverini, S., Apperley, J. F., ... & Hehlmann, R. (2013). European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. *Blood, The Journal of the American Society of Hematology*, *122*(6), 872-884.

[13] R Core Team. R: A language and environment for statistical computing [Internet]. Vienna, Austria: R Foundation for Statistical Computing; 2023. Available from: https://www.R-project.org/.

[14] Sjoberg, D. D., Whiting, K., Curry, M., Lavery, J. A., & Larmarange, J. (2021). Reproducible summary tables with the gtsummary package. *The R Journal*, *13*(1), 570-580.

[15] Li, N., Yang, X., Fan, L., Totev, T., Guerin, A., Chen, L., ... & Joseph, G. (2017). Nilotinib versus dasatinib as second-line therapy in patients with Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase who are resistant or intolerant to imatinib: a cost-effectiveness analysis based on real-world data. *Journal of Medical Economics*, *20*(4), 328-336.

[16] Cortes, J., Huynh, L., Mendelson, E., Brandt, P., Dalal, D., DerSarkissian, M., ... & Sheng Duh, M. (2020). Treatment patterns and deep molecular response in chronic phase–chronic myeloid leukemia patients treated with second-line nilotinib or dasatinib: a multi-country retrospective chart review study. *Leukemia & Lymphoma*, *61*(1), 98-107.

[17] Scalzulli, E., Caocci, G., Efficace, F., Rizzo, L., Colafigli, G., Di Prima, A., ... & Breccia, M. (2021). Real-life comparison of nilotinib versus dasatinib as second-line therapy in chronic phase chronic myeloid leukemia patients. *Annals of Hematology*, *100*, 1213-1219.

[18] Shah, N. P., Rousselot, P., Schiffer, C., Rea, D., Cortes, J. E., Milone, J., ... & Saglio, G. (2016). Dasatinib in imatinib-resistant or-intolerant chronic-phase, chronic myeloid leukemia patients: 7-year follow-up of study CA180-034. *American journal of hematology*, *91*(9), 869-874.

[19] Griffin, J. D., Guerin, A., Chen, L., Macalalad, A. R., Luo, J., Ionescu-Ittu, R., & Wu, E. Q. (2013). Comparing nilotinib with dasatinib as second-line therapies in patients with chronic myelogenous leukemia resistant or intolerant to imatinib–a retrospective chart review analysis. *Current medical research and opinion*, *29*(6), 623-631.

[20] Ćojbašić, I., Mačukanović-Golubović, L., Vučić, M., & Tijanić, I. (2017). Analyses of treatment outcome according to age in patients with chronic myeloid leukemia receiving front-line imatinib therapy. *Clinical Lymphoma Myeloma and Leukemia*, *17*(10), 696-702.