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Real-life comparison of Nilotinib versus Dasatinib as second-line therapy in chronic phase chronic myeloid leukemia patients

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Abstract

Introduction: Chronic myeloid leukemia (CML) is a rare hematologic malignancy whose management has been transformed by tyrosine kinase inhibitors (TKIs). After failure or intolerance to Imatinib, Dasatinib and Nilotinib are commonly used as second-line therapies. This study aimed to compare their tolerance and efficacy in real-world practice.

Patients and Methods: A retro-prospective study was conducted at the University Hospital of Oran (2013–2025), including 45 patients with chronic phase CML who switched from imatinib to a second-generation TKI (24 dasatinib, 21 nilotinib). Responses were assessed according to ELN 2020 and GAT-LMC criteria, toxicities were graded using CTCAE, and progression-free survival (PFS) and event-free survival (EFS) were analyzed using Kaplan-Meier.

Results and Discussion: The mean age was 45 years, and the main reason for switching was Imatinib resistance (84%). Regarding tolerance, Nilotinib was associated with metabolic and hepatobiliary toxicities (hyperbilirubinemia 19%),cutaneous toxicity (hyperkeratosis 19%), and cardiovascular toxicity (9.5%) , while Dasatinib was more frequently linked to anemia (25%) and pleural effusion (16.7%). Concerning molecular response, Nilotinib showed faster responses at 6 months (69% vs. 50% by ELN; 84.6% vs. 58.3% by GAT-LMC), but this trend reversed after 18 months, with better long-term response rates and persistence under Dasatinib. Survival analysis showed similar PFS between the two agents (101 months vs. 89.7 months; p = 0.880), while EFS favored Dasatinib (80 vs. 58.6 months). These findings suggest distinct response kinetics and safety profiles: Nilotinib induces earlier molecular responses but with more treatment interruptions, whereas Dasatinib ensures better long-term persistence.

Conclusion: In second-line therapy, Dasatinib and Nilotinib show comparable efficacy but distinct tolerance and response dynamics. Therapeutic choice should be individualized according to the patient's clinical and comorbidity profile: Nilotinib may be preferred for rapid molecular control, while Dasatinib appears better suited for long-term consolidation. These results highlight the importance of personalized follow-up in the management of CML in Algeria.

Keywords: Chronic myeloid leukemia; Tyrosine kinase inhibitors; Dasatinib; Nilotinib; Second-line therapy; Efficacy; Tolerance

1. Introduction

Chronic myeloid leukemia (CML) is a rare malignant hematologic disorder classified among the myeloproliferative neoplasms, with a global incidence estimated at 1 to 2 cases per 100,000 individuals. In Algeria, it ranks as the fifth most common cancer, with a steadily rising incidence from 0.4 cases per 100,000 in 2004 to 0.53 in 2014 [1,2].

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Biologically, CML is characterized by the presence of the Philadelphia chromosome (Ph), resulting from a reciprocal translocation between chromosomes 9 and 22 [t(9;22)]. This genetic abnormality leads to the fusion of the ABL oncogene from chromosome 9 with the BCR (Breakpoint Cluster Region) gene from chromosome 22, forming the BCR-ABL fusion gene. The resulting chimeric gene encodes an oncogenic protein with constitutively high tyrosine kinase (TK) activity, responsible for abnormal activation of intracellular signaling pathways involved in uncontrolled proliferation and prolonged survival of leukemic myeloid cells [3].

Historically, CML was associated with a poor prognosis, inevitably progressing to acute leukemia. This unfavorable trajectory was significantly altered by the emergence of targeted therapies, particularly tyrosine kinase inhibitors (TKIs). Imatinib, the first TKI launched in 2001, revolutionized the management of the disease by significantly improving survival compared to previous therapies such as interferon-alpha and cytarabine [4]. According to a recent update from the IRIS study, the 10-year overall survival with first-line Imatinib reaches nearly 80%. However, approximately 15 to 20% of patients develop resistance or intolerance to Imatinib, thereby requiring the use of a second-generation tyrosine kinase inhibitor (2G-TKI) [5].

The updated 2020 guidelines of the European LeukemiaNet (ELN) [6,7] define resistance based on the depth of molecular response in addition to complete hematologic response (CHR). Intolerance is defined by the occurrence of persistent or recurrent grade 3 or 4 adverse events despite appropriate co-medication or hygiene-dietary measures.

Nilotinib and Dasatinib, two second-generation TKIs, play a crucial role in the treatment of chronic-phase CML (CP-CML). These agents have demonstrated outstanding efficacy in both first- and second-line settings, inducing deeper and faster molecular responses and reducing progression to accelerated or blast phase compared to Imatinib [8].

Their superiority has been established in several randomized clinical trials involving newly diagnosed CP-CML patients, notably the ENESTnd (for Nilotinib) and DASISION (for Dasatinib) studies, where each TKI was compared to Imatinib. After 10 years of follow-up, these trials reported high cumulative rates of major molecular response (MMR)—88.2% for Dasatinib and 79.7% for Nilotinib—with similar overall survival rates: 89% for Dasatinib and 87.6% for Nilotinib [9,10]. However, real-world data directly comparing second-generation TKIs remain limited. Two recent studies—one retrospective and multicenter, the other monocentric—have confirmed comparable efficacy between Dasatinib and Nilotinib when used as second-line treatments [11,12].

The comparison of the efficacy and tolerability of Dasatinib and Nilotinib in the treatment of chronic-phase CML (CP-CML) is of major importance, particularly to optimize therapeutic decisions based on patients' clinical profiles [13]. In Algeria, these two second-generation TKIs are generally reserved for second-line use due to their high cost. The selection between Dasatinib and Nilotinib largely depends on individual clinical characteristics and the specific safety profile of each drug.

The objective of our study was to evaluate and compare, under real-world conditions, the efficacy and tolerability of Dasatinib and Nilotinib when used as second-line treatment in a monocentric cohort of CP-CML patients exhibiting resistance and/or intolerance to Imatinib.

2. Patients and Methods

This study is a retro-prospective, descriptive, and analytically oriented analysis conducted in the Hematology Department in collaboration with the Pharmacovigilance Unit of the University Hospital of Oran (EHU Oran), covering the period from January 1, 2013, to June 30, 2025. Included were patients over 18 years of age diagnosed with chronic-phase CML (CP-CML), initially treated with Imatinib as first-line therapy, and subsequently switched to a second-generation TKI (2G-TKI) due to resistance or intolerance. Eligible patients were required to have a regular and well-documented medical follow-up within the department, including molecular biology data available at least at two evaluation time points (6, 12, or 18 months). Non-inclusion criteria included patients in accelerated or blast phase at the time of treatment switch or those with incomplete medical records.

Data were collected from patients' medical records (follow-up sheets, biological tests, molecular results) and completed using a dedicated follow-up form. The variables analyzed included demographic characteristics, comorbidities, Sokal and EUTOS prognostic scores, BCR-ABL transcript type, the second-line TKI administered with initial dosage, reasons for switching, duration of exposure to treatment, and any treatment interruptions. Treatment responses were evaluated based on the updated criteria from the European LeukemiaNet (ELN 2020) [7] and The Algerian Working Group on LMC (GAT-LMC) [14], taking into account BCR-ABL levels at 3, 6, 12, 18, and 24 months, depending on the availability of molecular monitoring. Adverse events (AEs) occurring during second-line treatment were recorded and classified according to their severity using the Common Terminology Criteria for Adverse Events (CTCAE) [15].

Data analysis was conducted using an intention-to-treat approach to best reflect real-world treatment conditions. All patients initially assigned to either therapeutic group (Dasatinib or Nilotinib) were retained for longitudinal analysis of efficacy and tolerability, regardless of subsequent treatment modifications.

Patients who discontinued treatment before an evaluation point due to resistance were considered non-responders in response rate calculations. Those who stopped due to intolerance were classified as intolerant but were not counted as treatment failures. However, both profiles (resistance and intolerance) were included in the global longitudinal response analysis to avoid bias in interpreting therapeutic evolution. Conversely, patients still under treatment but lacking BCR-ABL quantification at a specific time point (due to logistical issues) were excluded from the response rate calculation at that particular time to limit bias from missing data.

Therapeutic efficacy was assessed through molecular responses at various time points, as well as progression-free survival (PFS) and event-free survival (EFS), both estimated using the Kaplan–Meier method, with survival curves compared via the Log-Rank test.Tolerability was evaluated by documenting adverse events, with a comparative analysis between the two treatment groups using Pearson's Chi-squared test. A p-value < 0.05 was considered statistically significant.

Table 1 Baseline demographic, clinical, and treatment characteristics

	Variable	**Effective Total (n=45)**	**% Total**	**Effective Dasatinib (n=24)**	**% Dasatinib**	**Effective Nilotinib (n=21)**	**% Nilotinib**
Gender	Male	26	57.8	14	58.3	12	57.1
	Female	19	42.2	10	41.7	9	42.9
Age groups	18–34 years	13	28.9	6	25.0	7	33.3
	35–49 years	14	31.1	8	33.3	6	28.6
	50–65 years	14	31.1	6	25.0	8	38.1
	>65 years	4	8.9	4	16.7	0	0.0
Transcript type	b2a2	18	40.0	11	45.8	7	33.3
	b3a2	15	33.3	7	29.2	8	38.1
	Mixed	4	8.9	2	8.3	2	9.5
Sokal Score	Low	7	17.1	3	14.3	4	20.0
	Intermediate	20	48.8	12	57.1	8	40.0
	High	14	34.1	6	28.6	8	40.0
Reason for switching from Imatinib to 2G TKI	Resistance	38	84.4	20	83.3	18	85.7
	Intolerance	5	11.1	3	12.5	2	9.5
	Mixed	2	4.4	1	4.2	1	4.8
Treatment discontinuation	Yes	22	48.9	11	45.8	11	52.4
	No	23	51.1	13	54.2	10	47.6
Reason for stopping 2nd-line treatment	Résistance	12	26.7	7	29.2	5	23.8
	Intolérance	8	17.8	3	12.5	5	23.8
	Mixte	2	4.4	1	4.2	1	4.8
Associated comorbidities	Diabetes	6	13.3				
	Hypertension	4	8.9				
	GI disorders	4	8.9				
	Others	3	6.7				

	Hypothyroidism	2	4.4		
	Epilepsy	1	2.2		
	Hypercholesterolemia	1	2.2		

Cross-tabulations were also conducted to explore the potential influence of specific clinical variables on treatment response and overall disease evolution.

All statistical analyses were performed using SPSS software (version 21) and Microsoft Excel.

3. Results

3.1. Description of the Study Cohort:

The study included 45 patients diagnosed with chronic-phase chronic myeloid leukemia (CML-CP) who were treated with a second-generation tyrosine kinase inhibitor (2G TKI): 24 patients (53.3%) received Dasatinib and 21 patients (46.7%) received Nilotinib. The mean age of the cohort was 45.6 years (median: 45), with a slight male predominance (57.8%), distributed evenly across both treatment groups. More than 90% of patients were under 65 years of age. The median duration of exposure to Imatinib before switching was 18 months (mean: 22 months). The main reason for switching to second-line therapy was resistance to Imatinib (84.4%), with a balanced distribution between the two 2G TKIs.

Data on BCR-ABL transcript types showed a predominance of b2a2 (40.0%), followed by b3a2 (33.3%) and the mixed b2a2 + b3a2 profile (8.9%). Regarding prognostic scores, 48.8% of patients were classified as intermediate-risk according to the Sokal score, and 70.7% as low-risk according to the EUTOS score. The Nilotinib group included more patients with high Sokal risk (40% vs. 28.6%).

The average duration of treatment with 2G TKIs was 49 months (median: 24 months), with a wide range from 1 to 150 months, reflecting significant heterogeneity in treatment maintenance. Nearly half of the patients (48.9%) discontinued second-line therapy, with a slightly higher rate in the Nilotinib group (52.4%) compared to the Dasatinib group (45.8%). The main reasons for discontinuation were resistance (26.7%) and intolerance (17.8%), with intolerance-related discontinuations more frequent under Nilotinib (23.8% vs. 12.5% under Dasatinib). The most common comorbidities included diabetes (13.3%), arterial hypertension (8.9%), and gastrointestinal disorders (8.9%) (Table 1).

3.2. Evaluation of Toxicities and Adverse Events:

The comparative analysis of toxicities revealed several differences between the two inhibitors. A significant elevation in bilirubin levels was observed under Nilotinib (19% vs. 0%; $p = 0.025$), suggesting moderate cholestatic hepatotoxicity. Other biochemical abnormalities were more frequently reported with Nilotinib, including elevated transaminases (9.5%), GGT (9.5% vs. 4.2%), ALP (4.8% vs. 4.2%), and hyperglycemia (9.5% vs. 4.2%), though these differences were not statistically significant.

Grade 2–3 anemia was significantly more frequent with Dasatinib (25.0% vs. 0%; $p = 0.048$), while severe thrombocytopenia was more common with Nilotinib (23.8% vs. 12.5%), without reaching statistical significance ($p = 0.270$). Neutropenia was moderate and comparable between both groups.

Hyperkeratosis was reported more frequently with Nilotinib (19.0% vs. 0%; $p = 0.025$), whereas pruritus (9.5% vs. 8.3%) and skin rashes (4.8% vs. 4.2%) were rare and similar in both groups. Regarding cardiopulmonary complications, Dasatinib was associated with a significantly higher rate of pleural effusions (16.7% vs. 0%; $p = 0.050$), often accompanied by dyspnea (16.7% vs. 4.8%), as well as edema and pulmonary arterial hypertension (8.3% each). In contrast, cardiovascular events occurred only under Nilotinib (9.5%).

Diarrhea was more common with Dasatinib (50% vs. 19%), while constipation (14.3% vs. 4.2%), anorexia (33.3% vs. 20.8%), and nausea (33.3% vs. 25.0%) were more frequently reported under Nilotinib, though without significant differences. Finally, arthralgia/myalgia was frequent in both groups (47.6% with Nilotinib vs. 41.7% with Dasatinib), and pronounced asthenia was more commonly reported under Nilotinib (76.2% vs. 50%; $p = 0.071$) (Table 2).

Table 2 Adverse Events and Toxicities by Treatment Group in the Study Population

Adverse Event	Total n (%)	Dasatinib n (%)	Nilotinib n (%)	p (Pearson Chi²)
↑ Transaminases	2 (4.4%)	0 (0.0%)	2 (9.5%)	0.302
↑ GGT	3 (6.7%)	1 (4.2%)	2 (9.5%)	0.472
↑ ALP	2 (4.4%)	1 (4.2%)	1 (4.8%)	0.362
↑ Bilirubin	4 (8.9%)	0 (0.0%)	4 (19.0%)	0.025*
Hyperlipasemia	2 (4.4%)	1 (4.2%)	1 (4.8%)	0.923
Hyperglycemia	3 (6.7%)	1 (4.2%)	2 (9.5%)	0.472
Thrombocytopenia	8 (17.8%)	3 (12.5%)	5 (23.8%)	0.270
Anemia	6 (13.3%)	6 (25.0%)	0 (0.0%)	0.048*
Neutropenia	6 (13.3%)	3 (12.5%)	3 (14.3%)	0.539
Pruritus	4 (8.9%)	2 (8.3%)	2 (9.5%)	0.889
Skin Rash	2 (4.4%)	1 (4.2%)	1 (4.8%)	0.365
Hyperkeratosis	4 (8.9%)	0 (0.0%)	4 (19.0%)	0.025*
Edema	2 (4.4%)	2 (8.3%)	0 (0.0%)	0.176
Pleural Effusion	4 (8.9%)	4 (16.7%)	0 (0.0%)	0.050*
Pulmonary Arterial Hypertension (PAH)	2 (4.4%)	2 (8.3%)	0 (0.0%)	0.176
Dyspnea	5 (11.1%)	4 (16.7%)	1 (4.8%)	0.205
Cough	3 (6.7%)	2 (8.3%)	1 (4.8%)	0.632
Cardiovascular Events	2 (4.4%)	0 (0.0%)	2 (9.5%)	0.122
Diarrhea	16 (35.6%)	12 (50.0%)	4 (19.0%)	0.228
Constipation	4 (8.9%)	1 (4.2%)	3 (14.3%)	0.234
Nausea	13 (28.9%)	6 (25.0%)	7 (33.3%)	0.538
Anorexia	12 (26.7%)	5 (20.8%)	7 (33.3%)	0.388
Arthralgia/Myalgia	20 (44.4%)	10 (41.7%)	10 (47.6%)	0.572
Asthenia	28 (62.2%)	12 (50.0%)	16 (76.2%)	0.071
Headache	7 (15.6%)	3 (12.5%)	4 (19.0%)	0.545
Paresthesia	5 (11.1%)	3 (12.5%)	2 (9.5%)	0.713
Weight Gain	4 (8.9%)	3 (12.5%)	1 (4.8%)	0.363
Epistaxis	2 (4.4%)	2 (8.3%)	0 (0.0%)	0.176

3.3. Evaluation of Treatment Response Over Time According to ELN and GAT-LMC Criteria

At 6 months, based on the 2020 ELN criteria, 60% of patients achieved an optimal response (BCR-ABL1 ≤ 1%), with an apparent advantage for Nilotinib (69.2%) over Dasatinib (50%). The rate of molecular failure was lower in the Nilotinib group (7.7% vs. 41.7%; p = 0.206). The GAT-LMC criteria, which are more permissive (target: BCR-ABL1 ≤ 10%), confirmed this trend, with 84.6% of patients achieving an optimal response under Nilotinib compared to 58.3% under Dasatinib (p = 0.104) (Figure 1).

At 12 months, major molecular response (MMR, BCR-ABL1 ≤ 0.1%) was achieved in 52.8% of patients, with a slight advantage for Nilotinib (55.6% vs. 50%). The failure rate remained higher in the Dasatinib group (38.9% vs. 16.7%; p =

0.327). Results according to the GAT-LMC criteria at 12 months (target: BCR-ABL1 ≤ 1%) showed a similar trend, with optimal response rates of 77.8% under Nilotinib and 55.6% under Dasatinib (p = 0.322) (Figure 2).

At 18 months, although the MMR was generally maintained (52.3%), a reversal of trend was observed, with higher response rates under Dasatinib (58.3% vs. 45.0%) and better tolerability (intolerance: 8.3% vs. 15.0%). By 24 months, Dasatinib continued to show a slight advantage in terms of response (52.4% vs. 35.3%) and tolerability (9.5% vs. 23.5%), although differences were not statistically significant (p = 0.406) (Figure 3).

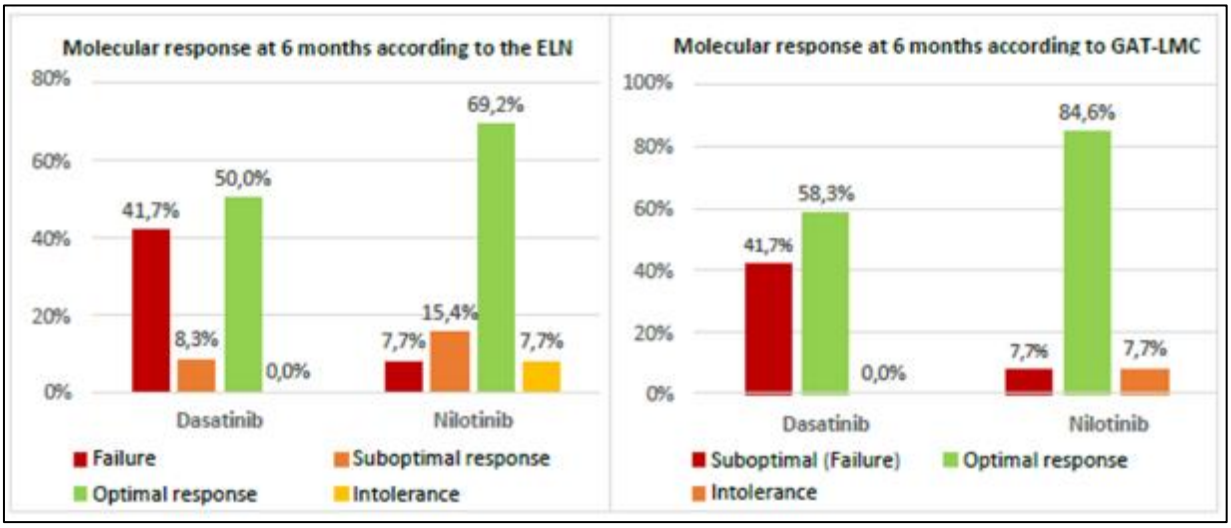


Figure 1 Molecular Response at 6 Months of Treatment

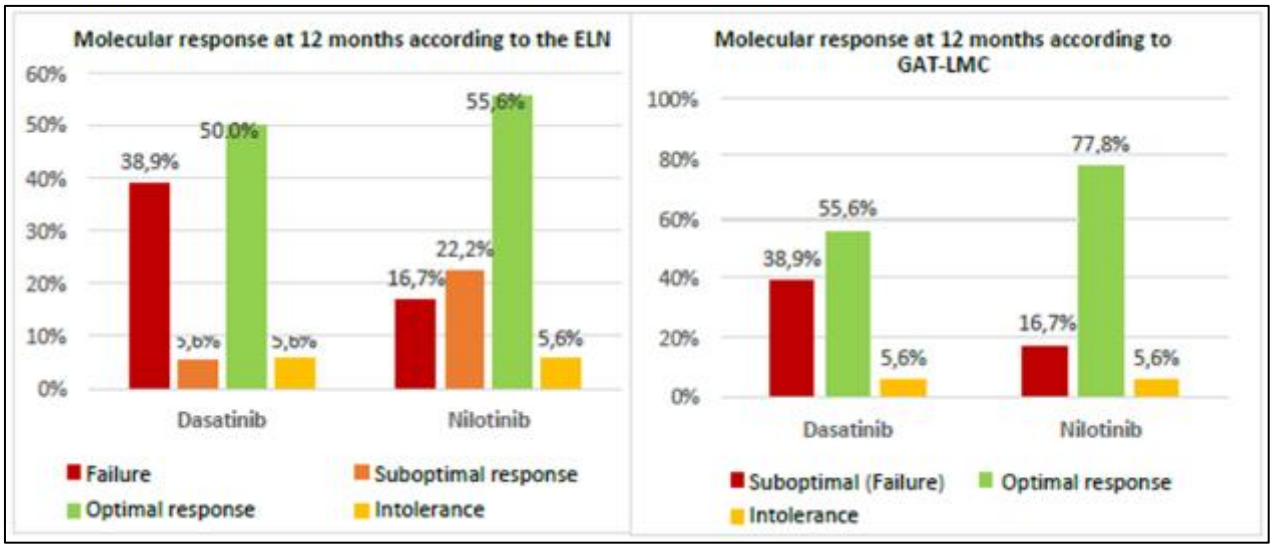


Figure 2 Molecular Response at 12 Months of Treatment

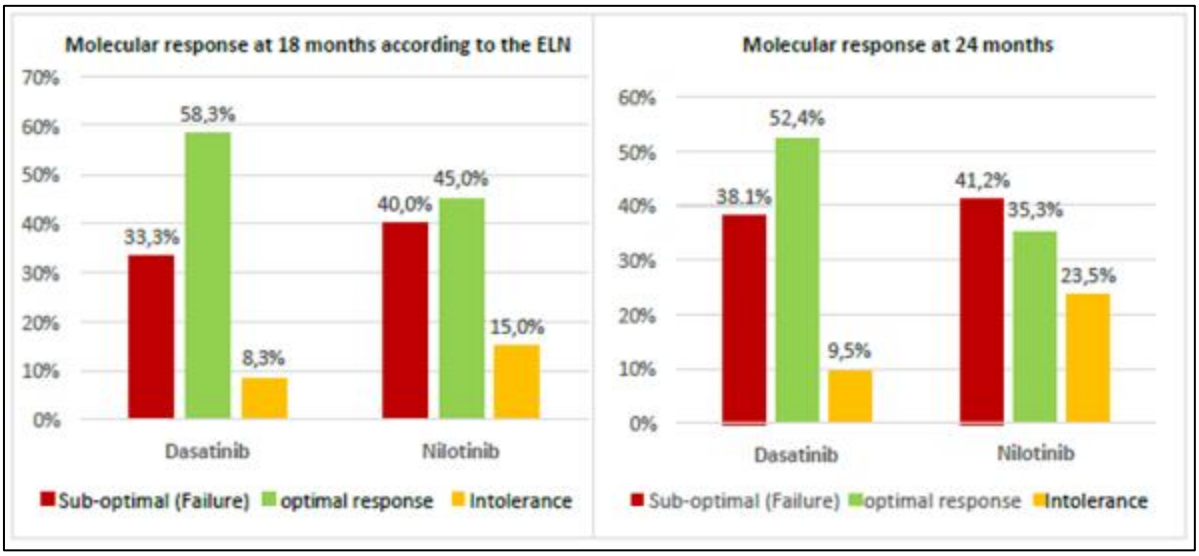


Figure 3 Molecular Response at 18 and 24 Months of Treatment

3.4. Analysis of Progression-Free and Event-Free Survival

The analysis of progression-free survival (PFS) by treatment group showed a mean duration of 101 months with Dasatinib (90% CI: 77.8–124) and 89.7 months with Nilotinib (90% CI: 69.3–110.1), with median values not reached in either group. At 24 months, PFS rates were estimated at 70.8% for Dasatinib and 73.1% for Nilotinib, with no significant difference ($p = 0.880$). Based on the reason for switching to a second-generation TKI, 24-month PFS was 70% in patients who switched due to resistance and 75% for those who switched due to intolerance, again with no significant difference ($p = 0.632$). In terms of gender, mean PFS was 93 months in females and 98 months in males ($p = 0.675$), with estimated 24-month PFS rates of 77.6% and 68.1%, respectively.

Analysis by BCR-ABL transcript type revealed a highly significant difference ($p < 0.001$). Patients with the b2a2 transcript had the best PFS (100 months), followed by those with b3a2 (89.8 months), while those with the mixed b2a2 + b3a2 transcript had markedly poor PFS (10.5 months, median of 7 months). At 24 months, PFS rates were estimated at 81.4% for b2a2, 73.3% for b3a2, and 0% for the mixed transcript group (Figure 4).

As for event-free survival (EFS), which includes both therapeutic failures and intolerances, the mean duration was 80 months with Dasatinib versus 58.6 months with Nilotinib ($p = 0.619$). The median was reached at 24 months with Nilotinib but not reached with Dasatinib. At 24 months, EFS rates were estimated at 54.2% for Dasatinib and 47.7% for Nilotinib. Finally, gender-based analysis showed a mean EFS of 78.9 months in females compared to 63.1 months in males, with 24-month rates of 60.6% and 42.3%, respectively ($p = 0.142$) (Figure 5).

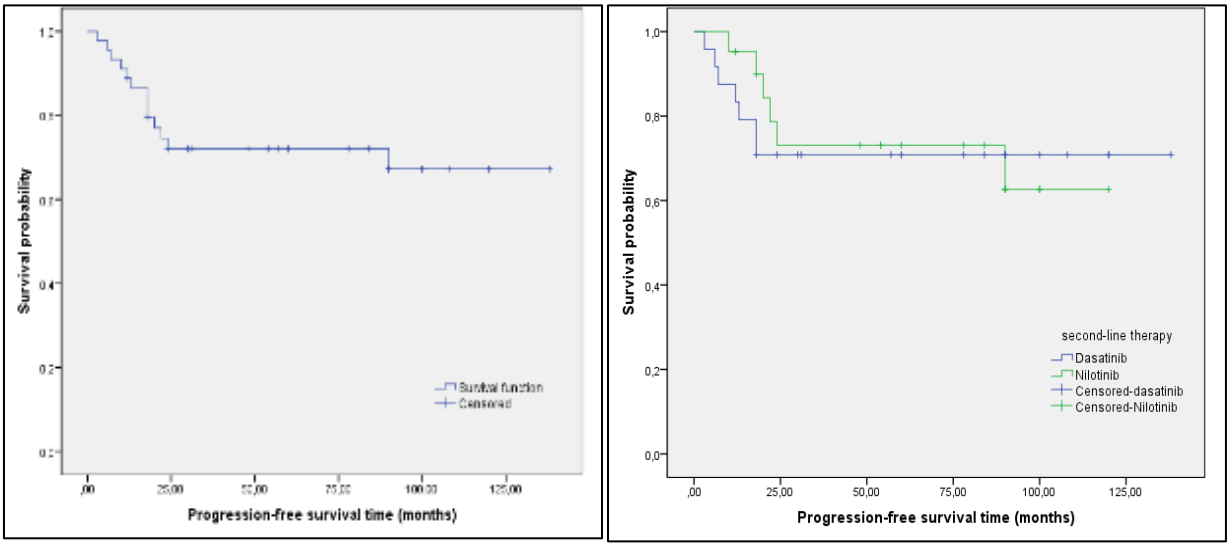
4. Discussion

The studied cohort was characterized by a relatively young average age (45 years), comparable to that reported by Scalzulli et al. [11] (49 years) and Toptas et al. [12] (50 years)—a factor often associated with better adherence and tolerance to TKIs. Most patients presented with a low EUTOS score, reflecting an overall favorable prognostic profile. However, a notable proportion exhibited high Sokal scores (40%), particularly in the Nilotinib group. This contrasts with the 9% reported in the study by Scalzulli et al. [11], suggesting a generally higher-risk population in our series.

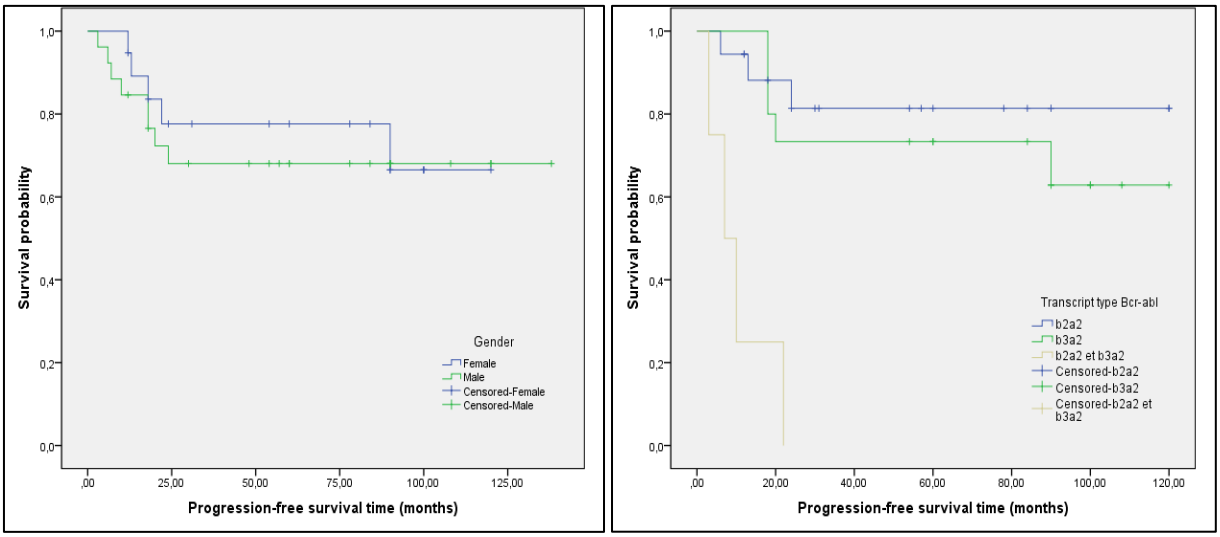
The median duration of exposure to Imatinib was relatively short (18 months), reflecting early treatment discontinuation due to therapeutic resistance—identified as the main reason for switching to second-generation TKIs in our cohort (84.4%), consistent with the rates reported by Scalzulli et al. [11] (83.2%) and Toptas et al. [12] (85%). This observation supports the idea that, in real-world clinical practice, most treatment switches are driven by therapeutic failure rather than intolerance.

The significant heterogeneity observed in the duration of second-generation TKI therapy (median 24 months, range 1 to 150 months) highlights the interindividual variability in treatment tolerance and efficacy. This finding aligns with data from Scalzulli et al. [11] (median 33 months, range 2–100) and Toptas et al. [12] (median of 5 years in both arms), confirming

that some patients achieve sustained disease control, while others discontinue treatment early due to failure or limiting side effects.

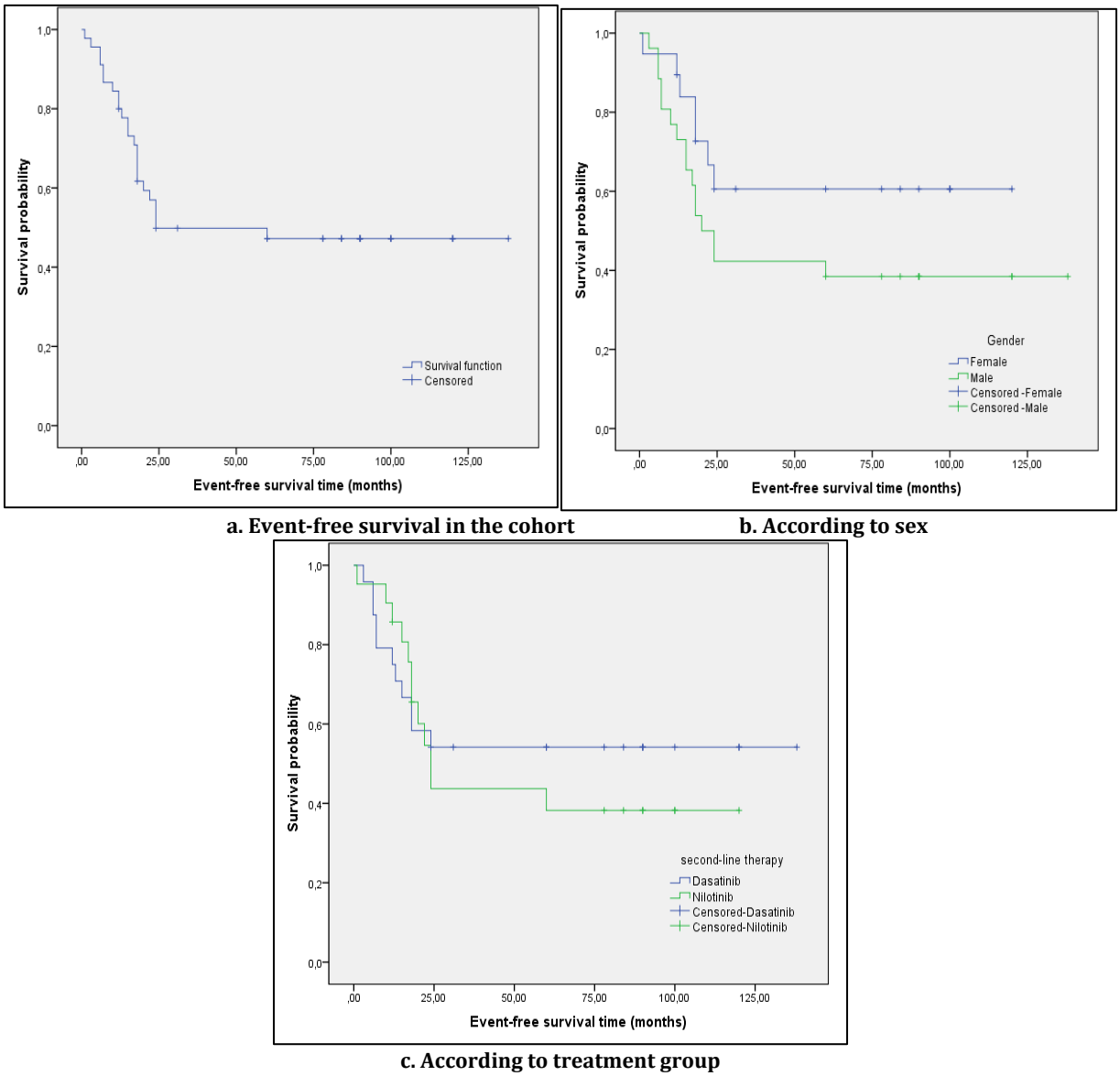


a. Progression-free survival in the cohort **b. According to treatment received**



c. According to sex **d. According to BCR-ABL transcript type**

Figure 4 Progression-Free Survival



a. Event-free survival in the cohort **b. According to sex**

c. According to treatment group

Figure 5 Event-Free Survival in the Cohort

The distribution of BCR-ABL transcripts in our cohort was typical, with a majority of b3a2 and b2a2 variants. However, mixed transcripts were observed in 8.9% of cases—more frequently than in Scalzulli et al. [11] (1.5%)—warranting particular attention due to their known association with poorer molecular prognosis and slower treatment response.

Regarding tolerance and therapeutic management of 2G TKIs, nearly half of the patients in our cohort (48.9%) discontinued treatment, reflecting a high rate of treatment withdrawals, more frequently observed in the Nilotinib group. The main reasons for discontinuation were resistance (26.7%) and intolerance (17.8%). Drug-specific analysis showed a higher rate of intolerance-related discontinuation with Nilotinib, suggesting a less favorable tolerance profile likely related to its metabolic and cardiovascular adverse effects.

In comparison, the study by Toptas et al. [12] reported similar discontinuation rates for Dasatinib (52.9% vs. 45.8%), while a more marked difference was observed for Nilotinib (30.8% vs. 52.4%). The study by Scalzulli et al. [11] reported an overall discontinuation rate due to intolerance of 13.7%, which was lower than in our cohort.

In our series, the notable prevalence of comorbidities (13.3% diabetes, 11.1% hypertension) underscores the need for rigorous multidisciplinary follow-up, particularly in patients treated with Nilotinib.

The comparative analysis of tolerance profiles highlights distinct toxicities between the two agents, which may strategically guide second-line therapeutic decisions. Nilotinib was associated with more pronounced hepatobiliary toxicity, with a significant elevation in bilirubin observed in our series (19% vs. 0%; p = 0.025), likely linked to inhibition of hepatocellular canalicular transporters [16]. Additional laboratory abnormalities—including elevations in transaminases (9.5%), GGT (9.5%), and ALP (4.8%)—were also more frequently observed with Nilotinib, though not statistically significant. This toxicity profile is consistent with the ENESTnd trial [9], which reported transient liver enzyme elevations in 8–15% of patients treated with Nilotinib. These findings advocate for close biochemical monitoring in patients with hepatic risk or polypharmacy.

Hematologically, the two agents present distinct profiles. In our cohort, Dasatinib was significantly associated with grade 2–3 anemia (25% vs. 0%; p = 0.048), indicating notable myelotoxicity—an effect well documented in the DASISION study [10], where severe cytopenias (primarily thrombocytopenia and neutropenia) were reported in 21% of patients. Nilotinib, for its part, induced severe thrombocytopenia in 23.8% of cases—a high rate but not significantly different from Dasatinib (12.5%; p = 0.270). These divergent toxicities must be weighed in patients with hematologic comorbidities or a history of toxicity under Imatinib.

Dermatologically, significant hyperkeratosis was observed under Nilotinib (19% vs. 0%; p = 0.025), a side effect rarely described in pivotal trials. Pruritus (9.5% vs. 8.3%) and cutaneous rashes (4.8% vs. 4.2%) were rare and comparable across both arms. Such skin reactions may impair treatment adherence and warrant dermatological management, especially in patients with a history of skin disorders.

Regarding pleuropulmonary and cardiovascular toxicity, Dasatinib was linked to a higher risk of pleural effusion (16.7% vs. 0%; p = 0.050), frequently accompanied by dyspnea. These dose-dependent effects were also reported in 52% of patients in the cohort of Scalzulli et al. [11] and in 41% of long-term follow-up in the DASISION study [10]. Conversely, in our cohort, Nilotinib was associated with major cardiovascular events in 9.5% of cases, consistent with findings from Toptas et al. [12] and the ENESTnd study [9], which reported up to 15% arterial events long-term, especially in patients with pre-existing risk factors. These findings underscore the need for rigorous cardiopulmonary risk stratification when initiating a 2G TKI.

Gastrointestinal disturbances were frequent but generally mild. Dasatinib was more often associated with diarrhea (50% vs. 19%), while Nilotinib induced higher rates of constipation (14.3%), anorexia (33.3%), and nausea (33.3%), without statistically significant differences. These side effects may impact quality of life and require proactive symptomatic management.

Finally, functional side effects such as arthralgia/myalgia were frequent in both groups, and marked asthenia was observed in 76.2% of patients receiving Nilotinib compared to 50% under Dasatinib (p = 0.071). Although not statistically significant, this difference could impact long-term adherence, particularly in elderly or multimorbid patients.

In summary, the differentiated tolerance profiles between the two second-generation TKIs should be a major consideration in second-line therapeutic decisions. Dasatinib may be preferable in patients with hepatic fragility or cardiovascular history, while Nilotinib may be suitable in the absence of arterial risk, though it requires close metabolic and hematological monitoring.

Data from our cohort revealed distinct molecular response kinetics between Dasatinib and Nilotinib in the second-line setting. As early as six months, Nilotinib showed a more rapid reduction in leukemic burden, with higher optimal response rates, whether by ELN 2020 criteria (69.2% vs. 50%) or the more permissive GAT-LMC thresholds (84.6% vs. 58.3%). Although these differences were not statistically significant, they reflect an enhanced early efficacy of Nilotinib, which could be advantageous in patients requiring rapid disease control or those at high risk of progression.

At 12 months, according to ELN 2020 criteria (BCR-ABL1 ≤ 0.1%), our study reported optimal response in 52.8% of patients, with comparable rates between Nilotinib (55.6%) and Dasatinib (50%). These results align with the trend reported by Scalzulli et al. [11], who found optimal response rates (MMR + MR4) of 65.2% for Dasatinib and 54.6% for Nilotinib. Despite a slight reversal in trends, performance remained relatively similar and not statistically different. Conversely, Toptas et al. [12] reported higher response rates: 73.5% under Dasatinib and 76.9% under Nilotinib achieved MMR at 12 months. These discrepancies may stem from methodological differences.

Unlike our intention-to-treat analysis, which includes patients who discontinued early due to failure or intolerance in the denominator when calculating response rates at each evaluation point, the studies by Scalzulli and Toptas appear to follow a per-protocol approach, excluding such cases. This methodological choice tends to overestimate response rates and could explain the higher outcomes reported in their findings.

At 18 months, a reversal in response dynamics was observed in our cohort, with a growing advantage in favor of Dasatinib: MMR was achieved in 58.3% vs. 45.0% under Nilotinib, a trend that persisted at 24 months. This shift suggests better therapeutic persistence under Dasatinib, likely linked to improved tolerance. Data from Scalzulli et al. [11] reported 24-month optimal response rates (MMR + MR4) of 70% for Dasatinib and 72% for Nilotinib. These substantially higher rates compared to our study (52.4% and 35.3%) further support the idea of selection bias stemming from excluding patients who discontinued treatment early.

Our results suggest that Nilotinib induces a more rapid molecular response during the first year, which may be relevant for patients requiring early molecular control, especially those with a high-risk profile (e.g., high Sokal score). In contrast, Dasatinib ensures better long-term molecular consolidation and a more favorable tolerance profile, making it suitable for older or comorbid patients. These crossed response kinetics underscore the importance of adaptive monitoring that considers both molecular response and individual tolerance to optimize second-line therapeutic strategies.

The analysis of progression-free survival (PFS) in our cohort confirms comparable efficacy between Dasatinib and Nilotinib as second-line therapies. At 24 months, PFS rates were similar—70.8% for Dasatinib versus 73.1% for Nilotinib ($p = 0.880$)—with median survival not reached in either group. These findings are consistent with those reported by Scalzulli et al. [11], who observed an overall PFS of 78.3%, with specific PFS rates of 84.1% under Nilotinib and 72% under Dasatinib, without significant difference. This alignment between studies reinforces the idea of long-term equivalence between the two second-generation TKIs in terms of disease progression control.

In our analysis, PFS did not appear to be significantly influenced by gender. However, the type of BCR-ABL transcript emerged as a critical prognostic factor: patients with the mixed b2a2 + b3a2 transcript showed markedly reduced PFS (median of 7 months), suggesting increased clonal instability. This highlights the importance of systematic molecular typing at diagnosis to guide early risk-adapted monitoring.

With regard to event-free survival (EFS), the data suggest better treatment persistence under Dasatinib, with a mean duration of 80 months versus 58.6 months for Nilotinib, and 24-month EFS rates of 54.2% and 47.7%, respectively. Although not statistically significant, this difference reflects a more favorable cumulative tolerance profile for Dasatinib. While Nilotinib performs well in terms of early molecular response, it may lead to more frequent early treatment discontinuations due to intolerance (23.8% vs. 12.5% under Dasatinib). This dissociation between PFS (efficacy) and EFS (efficacy plus tolerance) is pharmacotherapeutically relevant.

Lastly, a trend favoring female patients was observed in our cohort for EFS (60.6% vs. 42.3%), suggesting a potentially sex-influenced tolerance profile—an observation that warrants confirmation in larger cohorts.

5. Conclusion

Our real-world comparative study of second-generation tyrosine kinase inhibitors (TKI2G), Dasatinib and Nilotinib, as second-line treatments following Imatinib failure in chronic-phase chronic myeloid leukemia (CML-CP), highlights distinct pharmacodynamic and tolerability profiles but comparable overall efficacy.

Nilotinib stands out for its faster molecular response kinetics during the first 12 months, which may be advantageous for patients with high-risk disease or those requiring rapid molecular control. Conversely, Dasatinib demonstrates more sustained molecular response beyond 12 months, with higher rates of response maintenance and event-free survival (EFS). This crossover dynamic underscores the importance of personalized monitoring based on both therapeutic response and adverse event profiles.

In terms of safety, each molecule presents a distinct toxicity profile: Nilotinib is associated with more pronounced hepatobiliary and metabolic toxicity, as well as a non-negligible cardiovascular risk, while Dasatinib is more frequently linked to pleuropulmonary complications and hematologic myelotoxicity. These differences call for rigorous pre-treatment stratification, especially regarding hepatic, cardiovascular, and hematologic comorbidities.

Despite relatively high treatment discontinuation rates in our cohort a reflection of real-world clinical practice the 24 month progression-free survival (PFS) rates align with previously reported data, confirming similar medium-term efficacy between the two TKI2G agents. EFS, however, more clearly highlights the impact of tolerability on treatment persistence, with a trend favoring Dasatinib.

Lastly, our study emphasizes the value of integrating new prognostic markers, such as the type of BCR-ABL transcript, which showed a significant impact on PFS, as well as sex-based differences in tolerability, which could help guide more personalized treatment strategies in the future.

In conclusion, the choice between Dasatinib and Nilotinib as second-line therapy should be based on a comprehensive assessment of tolerability, patient comorbidities, and disease progression context. Our findings advocate for an individualized and dynamic approach, grounded in close monitoring of therapeutic response and adverse events, to optimize long-term management of CML patients.

Compliance with ethical standards

Disclosure of conflict of interest

The authors and all co-authors declare that they have no conflicts of interest in relation to this document.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

References

[1] Djouadi-Lahlou, K. (2010) Etude Epidemiologique Nationale de la Leucemie Myeloîde Chronique en Algerie: Travail Coopératif et Multicentrique sur une Période de 16 ans. A Propos 1927 Cas (1994-2009). Revue Algérienne d'Hématologie, 3, 6-10.

[2] Abdennebi N, Résultats à 12 ans du traitement de la leucémie myéloïde chronique (LMC) en 1ère phase chronique par l'Imatinib 400 mg (Imatib*), Revue Algérienne d'Hématologie, N° 13-14, Décembre 2017.

[3] Zerkout,S. Allogreffe de cellules souches hématopoïétiques (CSH) chez 23 patients atteints de Leucémie Myeloide Chronique (LMC) en phase avancée ou resistants / intolérants aux inhibiteurs de tyrosine kinase (ITK), Revue Algérienne d'Hématologie, N° 13-14, Décembre 2017.

[4] HughesTP,KaedaJ,BranfordS,etal. Frequency of major molecular responses to imatinib or interferon alfa plus cytarabine in newly diagnosed chronic mye loid leukemia. N Engl J Med 2003;349:1423-32.

[5] Hochhaus A, Larson RA, Guilhot F, Radich JP, Branford S, Hughes TP, Baccarani M, Deininger MW, Cervantes F, Fujihara S, Ortmann CE, Menssen HD, Kantarjian H,

[6] Baccarani M et al, European Leukemia Net recommendations for the management of CML 2013 .

[7] Hochhaus, A., Baccarani, M., Silver, R.T. et al.European LeukemiaNet recommendations for treating chronic myeloid leukemia 2020

[8] Tokuhira, M., Kimura, Y., Sugimoto, K., Nakazato, T., Ishikawa, M., Fujioka, I., ... & Kawaguchi, T. (2018). Efficacité et sécurité du traitement par nilotinib chez les patients atteints de leucémie myéloïde chronique nouvellement diagnostiquée en phase chronique. Oncologie médicale , 35 , 1-8.

[9] Saglio G, Kim DW, Issaragrisil S, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. N Engl J Med 2010;362:2251-9

[10] Kantarjian H, Shah NP, Hochhaus A, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med 2010; 362:2260-70

[11] Scalzulli E, Caocci G, Efficace F, et al. Real-life compari son of nilotinib versus dasatinib as second-line therapy in chronic phase chronic myeloid leukemia patients. Ann Hematol. 2021;100(5):1213–1219. doi:10. 1007/s00277-021-04477-0

[12] Second-line use of dasatinib and nilotinib in a real-world patient population with chronic phase chronic myeloid leukemia Tayfur Toptas, Derya Demirtas, Ahmet Mert Yanik, Ozlem Candan, Fatma Arikan, Secil Salim, Meral Menguc, Asu Fergun Yilmaz, Tulin Tuglular & Isik Kaygusuz Atagunduz.

[13] Adel, A., Abushanab, D., Hamad, A., Abdulla, M., Izham, M., & Yassin, M. (2021). Assessment of dasatinib versus nilotinib as upfront therapy for chronic phase of chronic myeloid leukemia in Qatar: a cost-effectiveness analysis. Cancer Control, 28, 10732748211001796.

[14] GAT-LMC, Société Algérienne d'Hématologie et de Transfusion Sanguine. Prise en chargedes patients atteints de leucémie myéloïde chronique en Algérie. Mise à jour des recommandations nationales. 5ème réunion , Workshop, 18 janvier 2018, Hôtel Mercure,Alger

[15] Common Terminology Criteria for Adverse Events V4.0 (CTCAE) 2009. Gradation toxicité.Traduit par la Fédération Francophone de Cancérologie Digestive (FFCD)