GSC Biological and Pharmaceutical Sciences
eISSN: 2581-3250 CODEN (USA): GBPSC2
Cross Ref DOI: 10.30574/gscbps
Journal homepage: https://gsconlinepress.com/journals/gscbps/

(RESEARCH ARTICLE)

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Cost Effectiveness Analysis of Tyrosine Kinase Inhibitors in the Management of Chronic Myeloid Leukemia

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GSC Biological and Pharmaceutical Sciences, 2025, 33(02), 082-092

Publication history: Received on 26 September 2025; revised on 01 November 2025; accepted on 04 November 2025

Article DOI: https://doi.org/10.30574/gscbps.2025.33.2.0430

Abstract

Introduction: Chronic myeloid leukemia (CML) prognosis has been dramatically improved by tyrosine kinase inhibitors (TKIs). Imatinib remains the standard first-line therapy, while Dasatinib and Nilotinib are used in cases of resistance or intolerance. Their high cost raises concerns of sustainability in resource-limited settings, justifying local pharmacoeconomic evaluations.

Patients and Methods: An observational study was conducted on 63 patients with chronic-phase CML. Quality of life was assessed using the EQ-5D, converted into QALYs. Direct medical costs (treatments, monitoring, adverse events) were collected over 12 months from two perspectives: hospital and societal. QALYs and costs were adjusted using regression analysis, and efficiency was measured through cost/QALY and ICUR.

Results/discussion: Imatinib showed the best cost-utility ratio in first-line therapy, with a cost/QALY well below the Algerian willingness-to-pay threshold (≈ 4,747 USD). Drug acquisition represented the main cost driver. In second-line therapy, Nilotinib provided only a limited benefit (+0.047 QALY) but with a substantial additional cost (~30,000 USD), resulting in an ICUR > 630,000 USD/QALY, far exceeding the threshold. Dasatinib thus appeared more cost-effective. Transition to second-line treatment and severe adverse events significantly impaired quality of life.

Conclusion: Imatinib remains the most cost-effective strategy in first-line therapy, while Dasatinib is economically more rational than Nilotinib in second-line therapy. The use of TKIs should balance clinical efficacy, quality of life, and economic sustainability.

Keywords: Pharmacoeconomic evaluations; Cost Effectiveness; Chronic myeloid leukemia; Tyrosine kinase inhibitors; QALYs; Quality of life

1. Introduction

Chronic myeloid leukemia (CML) is a rare hematologic malignancy, accounting for 7 to 15% of adult leukemias. In Algeria, its incidence has been rising, from 0.4 per 100,000 in 2004 to 0.53 per 100,000 in 2014 (1,2).

From a biological standpoint, CML is characterized by the presence of the Philadelphia chromosome, resulting from the translocation t(9;22)(q34;q11), which gives rise to the BCR-ABL1 fusion gene. This gene encodes a protein with

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constitutive tyrosine kinase activity, responsible for the aberrant activation of signaling pathways involved in leukemic cell proliferation and survival (3).

Prior to the advent of targeted therapies, CML carried a poor prognosis and typically progressed to acute leukemia. This course has been profoundly altered by the introduction of tyrosine kinase inhibitors (TKIs). Imatinib, the first TKI developed, represented a therapeutic breakthrough by specifically targeting the BCR-ABL protein, leading to high rates of cytogenetic and molecular responses and enabling overall survival rates close to those of the general population. Thanks to its sustained efficacy and acceptable tolerability, Imatinib remains the first-line reference treatment in our country (4).

However, approximately 20% of patients develop resistance or intolerance to Imatinib, requiring the use of second-generation TKIs, notably Dasatinib and Nilotinib (5,6). These agents have demonstrated faster and deeper molecular responses compared to Imatinib, along with a reduced risk of progression to accelerated or blast phase (7,8).

Thus, CML has become a chronic condition whose management relies on long-term, often lifelong, oral therapies. This shift has transformed the medical paradigm but has also raised a major challenge: the high and sustained cost of TKIs. Indeed, pharmacological treatment represents the largest share of expenditures, to which are added the costs of regular molecular monitoring, medical follow-up, and the management of adverse events (AEs).

In a resource-constrained setting such as Algeria, these cumulative costs place a significant burden on the healthcare system and raise concerns about budgetary sustainability and equitable access to treatment. As such, pharmacoeconomic analyses are essential to guide therapeutic choices.

Cost-utility analysis (CUA), based on the calculation of quality-adjusted life years (QALYs), is the gold-standard approach. It combines both duration and quality of life (QoL) into a single indicator, allowing the efficiency of different treatment strategies to be compared by accounting for both clinical benefits in terms of QoL and associated economic constraints (9).

Several international studies have assessed the cost-utility of TKIs, but their conclusions vary widely depending on local contexts, especially in relation to drug pricing, willingness-to-pay thresholds, and monitoring practices (10). In Algeria, available data remain scarce, despite the growing use of second-generation TKIs, which now calls for a rigorous assessment of their efficiency.

This study aims to determine the optimal positioning of tyrosine kinase inhibitors (Imatinib, Dasatinib, and Nilotinib) in the treatment of chronic-phase CML, taking into account their sequencing (first- and second-line), their impact on patient QoL, and the substantial costs associated with their use. In this context, the present study pursues two main objectives:

- To evaluate the cost-utility ratio of tyrosine kinase inhibitors in patients with chronic-phase CML.
- To identify, in second-line therapy, the most efficient strategy between Dasatinib and Nilotinib, used after failure or intolerance to Imatinib.

This study offers a twofold contribution. First, it provides robust local data from a real-life cohort of followed patients, complementing an abundant international literature that is often difficult to extrapolate to the Algerian healthcare and economic context. Second, it documents the relative economic burden of each therapeutic strategy and helps guide hospital decision-makers and health authorities toward a more efficient allocation of resources.

2. Patients and Methods

This study is a cost-utility pharmacoeconomic evaluation conducted among patients with chronic-phase chronic myeloid leukemia (CML), followed at the Hematology Department of the University Hospital of Oran between January and June 2025. It is an observational, cross-sectional study with a retrospective component, both descriptive and analytical in nature, aiming to estimate the cost-utility ratio of tyrosine kinase inhibitors (Imatinib, Dasatinib, and Nilotinib), and to identify, in second-line therapy, the most efficient strategy after failure or intolerance to Imatinib.

Included in the study were patients aged 18 years and over, diagnosed with chronic-phase CML confirmed by the presence of the Philadelphia chromosome or the BCR-ABL1 transcript, who had received continuous treatment with a TKI for at least twelve months, had complete clinical records, and had provided informed consent to participate in the

study. Exclusion criteria comprised patients in accelerated or blast phase, those unwilling to complete the questionnaires, and those whose medical data were incomplete or unusable.

Data collection relied on two complementary approaches: direct administration of questionnaires at inclusion, and review of medical records, allowing the capture of clinical, biological, economic, and quality-of-life (QoL) information. QoL was assessed using the generic EQ-5D-3L (EuroQol) questionnaire, widely employed in health economic evaluations. Patient preferences were converted into utility scores ranging from 0 (equivalent to death) to 1 (perfect health), using the French value set. Quality-adjusted life years (QALYs) were then calculated for each patient over a one-year period.

Adverse events (AEs) occurring during the twelve months prior to inclusion were classified using the CTCAE (Common Terminology Criteria for Adverse Events) and verified from medical records. Additional data collected included molecular response, presence of comorbidities, treatment duration, number of consultations, and additional diagnostic procedures.

Direct medical costs were estimated over a 12-month period from two perspectives: The hospital-based perspective, which included the cost of the prescribed TKI, specialist consultations, laboratory and imaging tests, and hospital-administered medications for the management of grade 3–4 AEs; and The combined perspective, which additionally incorporated outpatient costs borne directly by patients for managing grade 1–2 AEs.

Costs were expressed in Algerian dinars (DZD) based on hospital economic data, pharmacy retail prices, and national reference tariffs.

Statistical analysis was performed using SPSS version 27 and Microsoft Excel 2013. An initial descriptive phase characterized the study population by treatment group. Unadjusted QALYs and mean total costs per patient were calculated for each TKI group. To control for confounding related to patient heterogeneity, two multivariable models were developed.

The first, a multiple linear regression model, aimed to identify the factors influencing QALY variability. Explanatory variables included: TKI type, line of therapy, treatment response, treatment duration, age, sex, Sokal prognostic score, presence of comorbidities, and occurrence of grade 3–4 AEs. QALY means were then adjusted for demographic and clinical variables to isolate the treatment-specific effect on QoL.

The second, a Gamma regression model with log-link, was used to identify the main cost drivers and adjust average costs on the same explanatory variables, analyzing both perspectives (hospital-based and combined) separately. These models yielded adjusted means for QALYs and total costs per treatment group.

The cost-utility ratio (cost per QALY) and incremental cost-utility ratio (ICUR) were calculated from these adjusted means. The ICUR was interpreted according to the Algerian willingness-to-pay threshold of 4,747 USD/QALY. All statistical analyses were performed with a significance level of $p < 0.05$, and data were handled confidentially in accordance with the ethical principles of the Declaration of Helsinki.

3. Results

3.1. Description of the Study Population

The study population consisted of 63 patients diagnosed with chronic-phase CML, all of whom were receiving a tyrosine kinase inhibitor (TKI). Distribution by treatment showed 50.8% on Imatinib, 30.2% on Dasatinib, and 19% on Nilotinib, with a balanced proportion between first-line patients (Imatinib) and those receiving second-line therapy (Dasatinib or Nilotinib). The mean age was 53.2 ± 12.2 years.

Sex distribution revealed a female predominance in the cohort, with 63.5% women versus 36.5% men. This trend was particularly marked in the Imatinib (78.1%) and Nilotinib (66.7%) groups, whereas males predominated in the Dasatinib group (63.2%).

Analysis of the Sokal prognostic score showed a predominance of intermediate-risk profiles (46.7%), followed by both low- and high-risk profiles (26.6% each). This trend was observed in the Imatinib and Dasatinib groups, while the Nilotinib group showed an even distribution across the three risk categories (33.3% each).

Comorbidities were present in 44.4% of patients, with the highest prevalence in the Nilotinib group (66.7%), followed by the Imatinib (43.8%) and Dasatinib (31.6%) groups. The most common associated conditions were hypertension (20.6%) and diabetes (14.3%). (Table 1)

Molecular response at inclusion showed an optimal response rate of 98.3%, confirming the high effectiveness of TKIs in chronic-phase CML.

3.2. Adverse Events and Toxicities

The analysis of adverse events (AEs) by treatment group revealed a high overall incidence across all patients, with distinct safety profiles depending on the TKI administered.

Table 1 Demographic and Clinical Characteristics by TKI Treatment Group

Variables		**Imatinib (n = 32)**	**Dasatinib (n = 19)**	**Nilotinib (n = 12)**	**Total (n = 63)**
Age (years)		52,0 ± 12,7 [26–73]	52,6 ± 10,8 [24–68]	57,7 ± 13,0 [34–71]	53,2 ± 12,2 [24–73]
Gender	Female	25 (78,1 %)	7 (36,8 %)	8 (66,7 %)	40 (63,5 %)
	Male	7 (21,9 %)	12 (63,2 %)	4 (33,3 %)	23 (36,5 %)
Line of therapy		1st line: 32 (50,8 %)	2nd line: 31 (49,2 %)		/
Sokal score*	Low	8 (27,6 %)	4 (21,1 %)	4 (33,3 %)	16 (26,6 %)
	Intermediate	14 (48,3 %)	10 (52,6 %)	4 (33,3 %)	28 (46,7 %)
	High	7 (24,1 %)	5 (26,3 %)	4 (33,3 %)	16 (26,6 %)
Comorbidities		14 (43,8 %)	6 (31,6 %)	8 (66,7 %)	28 (44,4 %)
Type of comorbidities	Hypertension	6 (18,8 %)	5 (26,3 %)	2 (16,7 %)	13 (20,6 %)
	Diabetes	4 (12,5 %)	4 (21,1 %)	1 (8,3 %)	9 (14,3 %)
	Other conditions**	6 (18,8 %)	2 (10,5 %)	5 (41,7 %)	12 (19,0 %)
Optimal molecular response		31 / 31 (100 %)	16 / 17 (94,1 %)	11 / 11 (100 %)	58 / 59 (98,3 %)

* Sokal score assessed in 60 patients; ** Includes hypothyroidism, anemia, and other non-specific conditions.

Under Imatinib, nearly all patients experienced at least one AE, primarily asthenia (90.6%), myalgia/arthralgia (84.4%), and muscle cramps (68.8%). These toxicities were predominantly grade 1–2, reflecting good clinical tolerability. Severe events (grade 3–4) were less frequent.

In the Dasatinib group, AE frequency also remained high, with 68.4% reporting asthenia, 63.2% myalgia, and 36.8% cramps. This treatment was marked by a non-negligible proportion of grade 3–4 events, notably pleural effusion (15.8%) and pulmonary arterial hypertension (PAH, 5.3%)—well-documented and specific complications of this drug.

For Nilotinib, AE frequency was comparable, with 58.3% experiencing asthenia, 66.7% myalgia, and 50% cramps. This agent was distinguished by the occurrence of metabolic toxicities, such as hyperglycemia (16.7%), as well as hepatic (16.7%) and cardiac (8.3%) events.(Table 2)

This detailed characterization of safety profiles is a critical step in quantifying the cost implications of AE management, as part of the comprehensive cost-utility evaluation of tyrosine kinase inhibitors.

3.3. Quality of Life Assessment

The assessment of quality of life using the generic EQ-5D-3L questionnaire revealed a mean utility score of 0.63 ± 0.31, with values ranging from 0.013 to 1. This wide variability reflects significant heterogeneity in health perception among patients with chronic-phase CML. The mean QALYs, calculated over a one-year period, were also 0.63 ± 0.31.

Multivariable linear regression identified key factors influencing QoL. The occurrence of severe adverse events (grade 3/4) was the most significant negative predictor, associated with a substantial reduction in QALYs (B = –0.315; $p < 0.001$). In contrast, male sex was linked to slightly higher QALYs (B = +0.164; $p = 0.052$), and second-line treatment tended to be associated with lower QoL (B = –0.306; $p = 0.074$). Other variables, including age, comorbidities, Sokal score, and therapeutic response, were not significantly associated with QALY variation.(Table 3)

After adjustment for clinical and demographic covariates, estimated mean QALYs were 0.703 for Imatinib, 0.601 for Nilotinib, and 0.562 for Dasatinib. These findings confirm that Imatinib, used as a first-line agent, is associated with the best adjusted quality of life. Among second-generation TKIs, Nilotinib showed a slightly higher utility than Dasatinib, although the difference was not statistically significant. (Table 4)

Table 2 Summary of Adverse Events by Treatment and Severity

Adverse Event	Overall Cohort (%)	Imatinib (%)	Imatinib (G1+2 / G3+4)	Dasatinib (%)	Dasatinib (G1+2 / G3+4)	Nilotinib (%)	Nilotinib (G1+2 / G3+4)
Asthenia	77.7	90.6	59.4 / 31.2	68.4	36.8 / 31.6	58.3	25.0 / 33.3
Myalgia / Arthralgia	74.6	84.4	59.4 / 25.0	63.2	47.4 / 15.8	66.7	41.7 / 25.0
Cramps	55.2	68.8	56.3 / 12.5	36.8	21.1 / 15.8	50.0	25.0 / 25.0
Peripheral edema	30.3	40.6	40.6 / 0.0	15.8	15.8 / 0.0	41.7	41.7 / 0.0
Skin toxicity	31.7	31.2	31.2 / 0.0	31.6	31.6 / 0.0	33.3	33.3 / 0.0
Nausea / Vomiting	26.9	28.1	25.0 / 3.1	26.3	15.8 / 10.5	25.0	0.0 / 25.0
Diarrhea	17.5	12.5	6.2 / 6.2	36.8	31.6 / 5.3	0.0	0.0 / 0.0
Constipation	14.3	6.3	6.2 / 0.0	10.5	10.5 / 0.0	41.7	33.3 / 8.3
Anemia	12.7	15.6	9.4 / 6.2	10.5	10.5 / 0.0	8.3	8.3 / 0.0
Neutropenia	8.0	12.5	9.4 / 3.1	5.3	5.3 / 0.0	0.0	0.0 / 0.0
Thrombocytopenia	6.4	9.4	6.3 / 3.1	5.3	5.3 / 0.0	0.0	0.0 / 0.0
Hyperglycemia	3.2	0.0	0.0 / 0.0	0.0	0.0 / 0.0	16.7	0.0 / 16.7
Pleural effusion	4.8	0.0	0.0 / 0.0	15.8	0.0 / 15.8	0.0	0.0 / 0.0
PAH*	1.6	0.0	0.0 / 0.0	5.3	0.0 / 5.3	0.0	0.0 / 0.0
Hepatic toxicity	3.2	0.0	0.0 / 0.0	0.0	0.0 / 0.0	16.7	16.7 / 0.0
Cardiac toxicity	1.6	0.0	0.0 / 0.0	0.0	0.0 / 0.0	8.3	0.0 / 8.3

* PAH : Pulmonary arterial hypertension

Table 3 Results of the multivariate linear regression of factors influencing QALYs

Independent Variables	Coefficients (B)	p-value
(Constant)	0.608	0.001
Prescribed TKI treatment	0.139	0.193
Line of therapy	-0.306	0.074
Patient age	0.001	0.858
Patient sex	0.164	0.052

Time elapsed	0.001	0.278
Sokal score	0.067	0.168
Comorbidities	-0.024	0.750
Treatment response	-0.033	0.898
Grade 3/4 adverse events	-0.315	0.000

Table 4 Adjusted mean QALYs by treatment group

Prescribed TKI	**Adjusted Mean QALYs**	**95% confidence interval**	
		Lower Bound	**Upper Bound**
Imatinib	**0.703**	0.580	0.827
Dasatinib	**0.562**	0.412	0.713
Nilotinib	**0.601**	0.427	0.775

3.4. Direct Medical Cost Data

The economic evaluation of the cohort revealed a marked disparity in costs across the different TKIs, with drug acquisition representing the dominant component of overall expenditure. Imatinib remained by far the most affordable option (≈ 113,000 DZD per patient), while Dasatinib and Nilotinib generated significantly higher costs—approximately 2.1 million DZD and 5.67 million DZD, respectively—representing a 20- to 50-fold increase compared to Imatinib.

Costs related to specialist consultations, biological monitoring, and the hospital-based management of grade 3–4 adverse events remained low and accounted for only a marginal share of the total cost. In contrast, the outpatient management of grade 1–2 AEs—often borne directly by patients—averaged 6,994 DZD with Imatinib, 5,797 DZD with Dasatinib, and 7,907 DZD with Nilotinib. Integrating these additional expenses into the combined perspective allows for a more accurate representation of the actual economic burden associated with TKI-related toxicities. (Table 5)

Total cost analysis, performed using a Gamma-log regression model under both the hospital-based and combined perspectives, revealed that the type of TKI prescribed was the only statistically significant determinant of overall expenditures ($p < 0.001$). This finding highlights the predominant economic impact of drug acquisition costs in the management of CML. By contrast, all other demographic and clinical variables showed no significant influence on total costs, regardless of the analytical perspective considered. (Table 6)

Table 5 Gamma-log regression analysis of hospital-based and combined total costs

Variables	**Total Hospital Costs (p-value)**	**Total Combined Costs (p-value)**
Intercept	0.000	0.000
Prescribed TKI treatment	**0.000**	**0.000**
Patient sex	0.326	0.566
Comorbidities	0.099	0.198
Sokal score	0.178	0.277
Patient age	0.679	0.741
Grade 3/4 Adverse Events	0.832	0.778

After adjustment, the mean total costs under the hospital-based perspective were estimated at 114,687 DZD for Imatinib, 1.97 million DZD for Dasatinib, and 5.94 million DZD for Nilotinib—approximately 17 and 52 times higher than Imatinib, respectively.

Under the combined perspective, adjusted total costs reached 126,517 DZD, 2.01 million DZD, and 5.86 million DZD, respectively, confirming the substantial disparity between TKI-based treatment strategies. (Table 7)

Table 6 Direct medical cost data related to CML management

Type of Cost (in DZD)	Imatinib (mean ± SD)	Dasatinib (mean ± SD)	Nilotinib (mean ± SD)
Prescribed TKI	113 013 ± 19 061	2 102 637 ± 694 104	5 669 386 ± 887 369
Specialist Consultations	4 196 ± 1 068	3 651 ± 821	3 730 ± 1 190
Biological Monitoring	189 ± 58	173 ± 43	165 ± 65
Adverse Events (G3–4, Hospital)	1 042 ± 5 052	45 ± 183	197 ± 435
Adverse Events (G1–2, Ambulatory)	6 994 ± 12 239	5 797 ± 10 129	7 907 ± 12 356
Total Hospital Cost	115 437 ± 26,993	2 108 983 ± 697 442	5 673 189 ± 887 369
Total Combined Cost	128 618 ± 33 797	2 115 657 ± 693 134	5 682 544 ± 890 525

Table 7 Adjusted mean total costs by TKI and perspective

Prescribed TKI Treatment	Mean total Hospital Costs	95% CI		Mean total Combined Costs	95% CI	
		Lower	Upper		Lower	Upper
Imatinib	**114687,03**	101218,78	129947,38	**126516,92**	111678,49	143326,91
Dasatinib	**1974342,96**	1691974,88	2303834,51	**2012690,53**	1725936,51	2347087,00
Nilotinib	**5945423,89**	4945802,55	7147083,80	**5864652,77**	4889227,14	7034680,75

3.5. Pharmacoeconomic Analysis

The cost-utility analysis conducted from the hospital-based perspective showed that Imatinib, used as a first-line therapy, was associated with a favorable cost-utility ratio of 163,139.44 DZD/QALY (≈ 1,259.75 USD/QALY). In contrast, Dasatinib, used in second-line therapy, yielded a cost per QALY of approximately 3.51 million DZD/QALY (≈ 27,127.90 USD/QALY). Nilotinib resulted in a much less favorable cost-utility ratio, reaching 9.76 million DZD/QALY (≈ 75,386.86 USD/QALY).

Under the combined perspective, the findings confirmed the trends observed in the hospital-based analysis, with only minor differences in the cost estimates.

The cost-utility analysis using Dasatinib as the comparator in second-line treatment showed that Nilotinib provided an incremental gain of 0.047 QALY, but at the cost of an additional 3.97 million DZD (30,664.80 USD) from the hospital-based perspective, and 3.85 million DZD (29,744.88 USD) from the combined perspective.

The corresponding incremental cost-utility ratios (ICURs) were 8.45 million DZD/QALY (652,443 USD/QALY) and 8.19 million DZD/QALY (632,870 USD/QALY), respectively—both far exceeding the established willingness-to-pay threshold of 4,747 USD/QALY, based on Algeria's 2024 GDP per capita.

Given the near-identical results across both perspectives, the conclusion remains robust regardless of the analytical viewpoint adopted.

4. Discussion

Our cohort consisted of 63 patients with chronic-phase CML, evenly distributed between first-line treatment (50.8% on Imatinib, n = 32) and second-line treatment (49.2% on Dasatinib, n = 19; Nilotinib, n = 12). It is well established that approximately 20% of patients develop resistance or intolerance to Imatinib during follow-up, warranting the switch to a second-generation tyrosine kinase inhibitor (11). In our cohort, the main reason for initiating second-line therapy was resistance to Imatinib, observed in 84.4% of cases.

From a demographic standpoint, our cohort was characterized by a female predominance (63.5%), in contrast to pivotal trials, which reported a majority of male participants (62% in the IRIS trial (12), and 56–63% in DASISION(7). Additionally, the mean age in our study (53.2 years) was slightly higher than that reported in those trials (approximately 46–50 years).

Table 8 Evaluation of Cost-Utility Ratios

Treatment		**Mean Costs (DZD)**	**Mean Costs (USD)**	**Mean Utilities (QALYs)**	**Cost-Utility Ratio (DZD/QALY)**	**Cost-Utility Ratio (USD/QALY)**
Imatinib	Hospital scale	114 687,03	885,61	0.703	163 139,44	1 259,75
	Combined scale	126516,92	976,96		179 967,16	1 389,27
Dasatinib	Hospital scale	1 974342,96	15 245,89	0.562	3513065,76	27 127,91
	Combined scale	2012690,53	15 542,01		3 581299,87	27 654,82
Nilotinib	Hospital scale	5 945423,89	45 910,60	0.609	9 762600,80	75 386,86
	Combined scale	5 864652,77	45286,89		9 629971,70	74 362,70

Table 9 Incremental Cost-Utility Analysis Dasatinib vs. Nilotinib

Treatment Comparison	**Δ QALYs (12-month treatment)**	**Δ Costs (DZD)**	**ICUR (DZD/QALY)**	**ICUR (USD/QALY)**
Hospital Perspective	0.047	3 971080.33	84 491083,61	652 440,63
Combined Perspective		3 851962.24	81 956643,40	632 869,78

Regarding prognostic profile, the distribution of Sokal scores in our cohort showed a predominance of intermediate-risk patients (46.7%), while both low- and high-risk categories accounted for 26.6% each. This distribution is broadly consistent with those reported in pivotal trials such as ENESTnd (37% low, 35% intermediate, 28% high) and DASISION (33% low, 48% intermediate, c9% high) (7,8).

In our cohort, 44.4% of patients had comorbidities—most commonly hypertension (20.6%) and diabetes (14.3%)—a proportion notably higher than that observed in clinical trials (7,8, 12). This discrepancy reflects the difference between selected clinical trial populations and real-world practice, where chronic conditions are more common and may influence TKI tolerability, quality of life, and overall management costs.

In terms of tolerability, nearly all patients in our cohort experienced at least one adverse event (AE). The most frequent were fatigue (77.7%), musculoskeletal pain (74.6%), and cramps (55.2%), followed by peripheral edema (30.2%), skin toxicities (31.7%), and gastrointestinal disturbances. Hematologic toxicities—such as anemia (12.7%), neutropenia (8%), and thrombocytopenia (6.4%)—were less frequent, whereas specific AEs like pleural effusion with Dasatinib (15.8%) and metabolic or hepatic toxicities with Nilotinib (16.7%) confirmed previously documented safety profiles in the literature (7,8). Most AEs were grade 1–2, although grade 3–4 events were also observed.

These findings are consistent with those reported in pivotal trials: edema, cramps, and gastrointestinal symptoms were frequently reported in IRIS (60%, 49%, and 50%, respectively); pleural effusion was a hallmark AE of Dasatinib in the DASISION study (10%); and metabolic and hepatic toxicities were characteristic of Nilotinib in ENESTnd (grade 3–4 hyperglycemia: 5.4%; hepatic toxicity: 2.7%). However, our cohort showed a higher frequency of subjective symptoms such as fatigue and musculoskeletal pain—likely reflecting the burden of comorbidities and the representativeness of real-world clinical practice (7–12).

In our study, QALYs were calculated over a single one-year cycle using real-world data. This approach provides a direct estimate of health-adjusted life expectancy but does not capture longer-term therapeutic trajectories, which would require Markov modeling. The results revealed substantial variability, with QALYs ranging from 0.01 to 1, and a mean of 0.63 ± 0.31—corresponding to approximately 0.63 quality-adjusted life years over the observed period.

Multivariable analysis identified the main determinants of quality of life. Grade 3/4 toxicities had the strongest impact, reducing QALYs by an average of 0.315 ($p < 0.001$), confirming their central role in deteriorating health-related quality of life. Sex also appeared influential: male patients had on average 0.164 more QALYs than females ($p = 0.052$), a result near the threshold of significance and possibly related to biological or psychosocial differences in treatment perception and tolerance. Treatment line also affected outcomes—second-line patients had 0.306 fewer QALYs on average compared to those on first-line therapy ($p = 0.074$). Indeed, switching to second-line treatment after failure or intolerance to Imatinib corresponds to a more physically and psychologically demanding treatment phase, which likely contributes to a less favorable perception of overall health.

In contrast, treatment response and the presence of comorbidities were not significantly associated with QALYs, although a trend toward lower utility scores was observed in these subgroups. The lack of significance may be due to the sample size. Similarly, age, follow-up duration, and Sokal score showed no notable effect, suggesting that intercurrent clinical events—such as severe toxicities or treatment shifts—are the primary factors shaping patients' quality of life.

To isolate the specific impact of treatment on quality of life, an adjusted analysis was performed controlling for clinical and demographic variables, while excluding those directly influenced by treatment (therapeutic response, severe toxicities, and treatment line). The adjusted QALY scores showed that Imatinib had the highest mean (0.703 QALYs), confirming its better tolerability and more favorable impact on quality of life when used as a first-line therapy. Second-generation TKIs yielded lower scores, though the difference between them was moderate; Nilotinib appeared slightly more favorable (0.601 QALYs) compared to Dasatinib (0.562 QALYs). These results are consistent with earlier observations indicating that switching to second-line therapy is a major determinant of reduced QALYs.

The economic evaluation conducted in our cohort highlighted the predominant weight of drug acquisition costs in CML management. Generic Imatinib remained by far the most affordable option, with a mean acquisition cost estimated at 113,000 DZD per patient, whereas Dasatinib and Nilotinib reached approximately 2.1 million DZD and 5.67 million DZD, respectively—about 20 and 50 times more expensive. These disparities underscore the significant economic gap between first- and second-generation TKIs and illustrate the critical influence of treatment choice on overall expenditures.

Other medical follow-up components (specialist consultations, laboratory monitoring) remained limited and relatively uniform across groups, contributing only marginally to total cost. In contrast, adverse event (AE) management revealed greater variability. Grade 3–4 AEs generated modest hospital-based costs, as a substantial proportion were handled in the outpatient setting. At this level, the out-of-pocket expenses borne by patients for the management of grade 1–2 AEs (and sometimes grade 3) were significant: ≈6,994 DZD under Imatinib, 5,797 DZD under Dasatinib, and 7,907 DZD under Nilotinib. This reflects a partial shift of the economic burden toward patients, especially for chronic or recurrent toxicities. Incorporating the combined perspective, which integrates both hospital-based and outpatient costs, provides a more accurate picture of the real economic burden of the disease.

Regression analysis confirmed that the type of TKI was the only significant determinant of overall costs ($p < 0.001$), while other variables (age, sex, Sokal score, severe AEs) had no substantial impact. Comorbidities showed only a non-significant trend toward increased costs. After adjustment, Imatinib remained the most cost-effective strategy, with a mean hospital-based cost of 114,687 DZD, compared to 1.97 million DZD for Dasatinib and 5.94 million DZD for Nilotinib. The same hierarchy was observed under the combined perspective, where costs for Dasatinib and Nilotinib were approximately 16 and 46 times higher, respectively, than those for Imatinib. The difference between the two perspectives remained modest, confirming that additional patient-borne expenses represent a relatively small proportion compared to the drug acquisition costs.

The pharmacoeconomic analysis demonstrated that Imatinib maintained a highly favorable cost-utility profile in first-line therapy, with an estimated cost of approximately 179,967 DZD/QALY (≈ 1,389 USD/QALY), well below the Algerian willingness-to-pay threshold (≈ 4,747 USD/QALY) (13). These results confirm Imatinib's position as the most efficient option for initiating treatment. Similar conclusions were reported by Nguyen et al. (2020) in the United States (14), who, using a one-year decision-analytic model, showed that generic Imatinib was the dominant strategy compared to second-generation TKIs, with an average cost of 55,331 USD for 0.773 QALYs, resulting in a significantly more favorable cost per QALY than Dasatinib or Nilotinib. Likewise, the South African study by Woudberg et al. (2025) (15), based on a 20-year Markov model, also concluded that generic Imatinib remained the most cost-effective and sustainable first-line treatment, yielding 5.93 QALYs for a cost of 120,720 USD, whereas Dasatinib and Nilotinib, although associated with additional QALY gains, far exceeded the national cost-effectiveness threshold (18,760 USD/QALY). Thus, in three

distinct economic settings—Algeria, the United States, and South Africa—Imatinib consistently emerges as the most efficient first-line strategy, reinforcing its status as the reference standard in initial CML management.

In second-line therapy, our analysis showed that Nilotinib provided a modest incremental benefit of 0.047 QALYs over Dasatinib, but at an additional cost of approximately 30,000 USD, resulting in an extremely unfavorable ICUR of around 633,000 USD/QALY—far above the Algerian acceptability threshold (≈ 4,747 USD/QALY). These findings highlight the superior relative efficiency of Dasatinib in our cohort (≈27,127 USD/QALY vs. ≈75,386 USD/QALY for Nilotinib). Similar observations were reported by Kulpeng et al. (2014) in Thailand (16): in a lifetime Markov model, Nilotinib yielded an incremental gain of 0.44 QALYs, but at a cost of nearly 59,000 USD, corresponding to an ICER of approximately 132,000 USD/QALY, which exceeded the local threshold (≈ 3,870 USD/QALY), again confirming the economic advantage of Dasatinib in second-line therapy.

In contrast, the results of Bonifacio et al. (2022) in Italy (17) point in the opposite direction. In a 40-year economic model, Nilotinib appeared dominant over Dasatinib, with a gain of +1.89 QALYs and a cost reduction estimated at –€38,760 per patient. This divergence is mainly attributed to methodological differences and the relative TKI prices on the Italian market, which are markedly different from those observed in Algeria.

5. Conclusion

This study represents one of the first cost-utility-based pharmacoeconomic evaluations of tyrosine kinase inhibitors (TKIs) for the management of chronic myeloid leukemia (CML) in Algeria. Conducted on a real-world cohort of 63 patients followed at the University Hospital Center (EHU) of Oran, it provides original local data in a field where national literature remains scarce.

Our findings highlight the central role of Imatinib in first-line therapy. Associated with the highest quality-adjusted life years (QALYs) and the lowest treatment costs, it offers a highly favorable cost-utility ratio, well below the Algerian willingness-to-pay threshold. These data confirm its relevance as the standard initial treatment, further supported by the availability of affordable generic formulations.

In contrast, second-generation TKIs (Dasatinib and Nilotinib) are associated with significantly higher costs—20 to 50 times greater than Imatinib. From a quality-of-life standpoint, switching to second-line therapy represents a more physically and psychologically demanding treatment phase, contributing to a lower overall health perception. Incremental analysis shows that although Nilotinib offers a slight QALY gain over Dasatinib, this benefit comes at a disproportionate cost (ICUR > 630,000 USD/QALY). In the Algerian context, Dasatinib thus emerges as the most efficient second-line option after Imatinib failure or intolerance.

Furthermore, our analyses confirm the substantial negative impact of grade 3–4 adverse events on quality of life, as well as the economic burden of their management—often partially borne by patients. These findings emphasize the importance of an integrated approach in which economic evaluation complements clinical efficacy to guide treatment decisions.

In conclusion, Imatinib remains the most efficient first-line agent, while Dasatinib stands as the most rational second-line option. Nevertheless, further studies using longer time horizons (e.g., Markov modeling) are needed to validate these results. This work contributes to informing health policy decisions in Algeria and underscores the need to strengthen pharmacoeconomic evaluations to optimize resource allocation and ensure the sustainability of the healthcare system in the face of rising costs of innovative therapies.

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.

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