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ORIGINAL RESEARCH

Safety and Efficacy of Flumatinib in Patients with Chronic Phase Chronic Myeloid Leukemia: A Real-Life Cohort Observational Study

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Background: This study aims to comprehensively evaluate the safety and effectiveness of flumatinib in both first-line and subsequent-line therapies in 244 chronic-phase chronic myeloid leukemia (CML-CP) patients.

Methods: Response criteria were applied according to the European LeukemiaNet. Adverse events (AEs) occurring after flumatinib treatment were documented and graded for severity.

Results: The study encompassed 244 patients with CML-CP, stratified by treatment lines: first-line (1L, N=138), second-line (2L, N=63), and third-line or above (≥3L, N=43). First-line flumatinib therapy resulted in a major molecular response achieved by 50.7% at 6 months and 66.7% at 12 months, with a deep molecular response (DMR) achieved by 20.3% at 6 months and 35.5% at 12 months. In subsequent treatment lines, those with baseline MR2 had a DMR rate of 42.9%, compared to 23.3% for those without it. Significant differences in molecular response rates were observed based on treatment line and prior tyrosine kinase inhibitors (TKI) resistance ($p<0.05$). However, subgroup analyses showed no significant differences in treatment responses between the warning and resistance groups after flumatinib therapy. Dose reduction strategies, implemented in 19.3% of patients, have proven feasible without compromising efficacy. Eight patients subsequently attempted treatment cessation, with five maintaining treatment-free remission. AEs were predominantly grade 1–2, with diarrhea (27.0%), fatigue (12.3%), and thrombocytopenia (11.5%) being the most frequent. Grade 3/4 AEs were infrequent, highlighting flumatinib's manageable safety profile.

Conclusion: Flumatinib displays significant clinical efficacy and a superior safety profile compared to other second-generation TKI, whether administered in first-line or subsequent treatment settings.

Keywords: chronic myeloid leukemia, flumatinib, clinical response, safety, chronic phase

Introduction

Chronic myeloid leukemia (CML) is a hematologic malignancy characterized by the constitutive activity of the *BCR::ABL1* fusion oncoprotein, representing approximately 15% of adult leukemia cases globally.[1] The introduction of tyrosine kinase inhibitors (TKI) has significantly transformed CML treatment, converting this previously fatal disease into a manageable chronic condition.[2,3] While the first-generation (1G) TKI, imatinib, established the initial treatment standard, approximately 30–40% of patients exhibit suboptimal responses or develop resistance,[4,5] creating an urgent need for more effective therapeutic alternatives.

Second-generation (2G) TKIs, such as nilotinib and dasatinib, have shown superior efficacy in achieving deep molecular responses (DMR) and overcoming imatinib resistance.[6–9] However, their clinical utility is hampered by notable off-target toxicities, including cardiovascular events[10] and pleural effusion.[11] This challenge of balancing therapeutic efficacy with safety concerns highlights the pressing need for agents with optimized therapeutic indices. Flumatinib, a novel second-generation TKI that is highly selective for *BCR::ABL1*, was developed to address these limitations. Phase III clinical trials demonstrated flumatinib's superiority over imatinib in the first-line treatment of newly

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diagnosed chronic-phase CML (CML-CP), achieving significantly higher major molecular response (MMR) rates at 12 months (33.7% vs 18.3%) and progressively DMR over 2 years.[12] Consequently, flumatinib received approval in China in 2019 for the first-line treatment of CML-CP.[13]

Despite these advancements, the clinical use of flumatinib has a relatively brief history, and real-world data regarding its efficacy and safety in treating CML-CP, alongside clinically pertinent dilemmas (such as dose optimization strategies under intolerance circumstances and feasibility of treatment-free remission attempts) remain limited. This study aimed to conduct a comprehensive evaluation of flumatinib's safety and efficacy in both first-line and subsequent-line therapeutic settings through retrospective real-world cohort analysis, while empirically validating the clinical feasibility of its dose optimization strategy to facilitate personalized therapeutic decision-making.

Methods

Patients

CML-CP patients who received flumatinib treatment from January 2019 to August 2024 were enrolled in this study. Inclusion criteria comprised an age of over 18 years, a diagnosis of CML-CP, and a duration of flumatinib therapy exceeding one year. Patients diagnosed with accelerated phase or blast phase, as well as those with incomplete data, were excluded from the analysis. A total of 244 patients were included, comprising 150 (61.5%) males. The median age was 38 years, with an age range of 18 to 72 years. The study was approved by the Institutional Ethics Committee of Tongji Medical College at Huazhong University of Science and Technology (Wuhan, China) (reference number [2023] 0814) and adhered to the guidelines of the Declaration of Helsinki. Informed consent was waived due to the retrospective nature of the study. Basic patient information, laboratory findings, medication records, adverse events (AEs), and other clinical data were collected during regular outpatient follow-ups.

Clinical Response Assessment

CML-CP is characterized by the presence of less than 10% blasts in either the peripheral blood or bone marrow, alongside the absence of extramedullary involvement. The clinical response of patients to flumatinib treatment is assessed through cytogenetic and molecular tests measuring *BCR::ABL1* mRNA levels. Responses are classified into three categories—optimal response, suboptimal response, and treatment failure—based on cytogenetic and molecular responses evaluated at 3, 6, and 12 months following treatment, in accordance with the European LeukemiaNet (ELN) 2020 guideline.[14] An optimal response is defined as *BCR::ABL1* ^{IS} levels of ≤10%, ≤1%, and ≤0.1% at 3, 6, and ≥12 months, respectively. A warning is indicated by *BCR::ABL1*^{IS} levels of >10%, >1% to 10%, and >0.1% to 1% at the same time points. Failure is defined as *BCR::ABL1*^{IS} levels exceeding 10% at 3 months, confirmed within 1 to 3 months, as well as levels exceeding 10% at 6 months and >1% at 12 months or any subsequent time. A complete cytogenetic response (CCyR) is indicated by 0% Philadelphia chromosome-positive (Ph+) metaphases in the bone marrow. MMR is defined as *BCR::ABL1*^{IS} ≤0.1%, while DMR refers to MMR4.0, which is characterized by *BCR::ABL1* ^{IS} ≤0.01%.

Adverse Events

Patients were regularly monitored for hematological and biochemical assessments. AEs occurring after flumatinib treatment were documented, including hematological toxicities (leukopenia or neutropenia, thrombocytopenia, and anemia), gastrointestinal symptoms (nausea and vomiting, diarrhea, constipation, and gastrointestinal discomfort), rash, fatigue, musculoskeletal pain, and hepatobiliary and elevated creatinine. The severity of these AEs was graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

Statistical Analysis

Categorical variables were expressed as frequencies and percentages. For continuous data that followed a normal distribution, means and standard deviations were reported; otherwise, medians and interquartile ranges (IQR) were provided. Comparisons of categorical variables were performed using either Pearson's chi-square test or Fisher's exact

test. Statistical analyses were conducted using IBM SPSS Statistics (version 25.0; IBM Corp., Armonk, NY, USA), and a p-value of less than 0.05 was considered statistically significant.

Results

Patient Characteristics

The study included 244 patients with CML-CP, categorized according to the line of flumatinib treatment: first-line (1L, N=138), second-line (2L, N=63), and third-line or above (≥3L, N=43). The detailed patient disposition is presented in Table 1. Overall, male patients predominated within all cohorts (1L: 65.2%; 2L: 66.7%; ≥3L: 58.1%). The median ages at diagnosis were 36 years (IQR 30–50) for 1L, 42 years (30–53) for 2L, and 38.5 years (28–47.5) for patients in the ≥3L category. The median duration of TKI therapy increased with later treatment lines: 2.48 years (1.43–3.57) for 1L, 4.99 years (3.84–6.70) for 2L, and 7.46 years (6.61–10.31) for patients in the ≥3L group. Comorbidities were present in 21.0% of the 1L cohort, 23.8% of the 2L cohort, and 14.0% of the ≥3L patients. Most patients were diagnosed as low-risk (Sokal score). In the 1L cohort (118 evaluable patients), 74 (53.6%) were classified as low-risk; among the 2L patients (56 evaluable), 37 (58.7%) were low-risk; and in the ≥3L group (38 evaluable), 26 (60.5%) were categorized as low-risk.

Table 1 Demographic and Clinical Characteristics of Patients with Chronic Myeloid Leukemia

Characteristics	1st Line (N=138)	2nd Line (N=63)	3rd Line or Above (N=43)
Male, N (%)	90 (65.2)	42 (66.7)	25 (58.1)
Age at diagnosis, years, median (IQR)	36 (30–50)	42 (30–53)	38.5 (28–47.5)
Age at diagnosis, years, median (range)	36 (18–70)	42 (18–72)	38.5 (18–64)
TKIs therapy duration, years, median (IQR)	2.48 (1.43–3.57)	4.99 (3.84–6.70)	7.46 (6.61–10.31)
Comorbidity, N (%)	29 (21.0)	15 (23.8)	6 (14.0)
Sokal score, N (%)			
Low	74 (53.6)	37 (58.7)	26 (60.5)
Intermediate	31 (22.5)	12 (19.0)	10 (23.3)
High	13 (9.4)	7 (11.1)	2 (4.7)
Unknown	20 (14.5)	7 (11.1)	5 (11.5)
ELTS score, N (%)			
Low	89 (64.5)	35 (55.6)	30 (69.8)
Intermediate	23 (16.7)	8 (12.7)	6 (14.0)
High	6 (4.3)	3 (4.8)	2 (4.7)
Unknown	20 (14.5)	7 (11.1)	5 (11.5)
Prior TKI, N (%)			
Imatinib	–	47 (74.6)	1 (2.3)
Dasatinib	–	6 (9.5)	34 (79.1)
Nilotinib	–	10 (15.9)	8 (18.6)
Resistant to prior TKI, N (%)			
Imatinib	–	39 (61.9)[a]	3 (7.0)[b]
2G TKI	–	10 (15.9)	3 (7.0)
1G and 2G TKI	–	–	36 (83.7)
Response at baseline, N (%)			
<MR1	–	22 (34.9)	6 (14.0)
MR1-MR2	–	6 (9.5)	9 (20.9)
MR2-MMR		20 (31.7)	21 (48.9)
MMR	–	9 (14.3)	5 (11.6)
MR4 or DMR	–	6 (9.5)	2 (4.7)

Notes: [a] 14 patients underwent second-line treatment due to first-line intolerance. [b] 1 patient developed intolerance to both imatinib and dasatinib, while 3 patients developed resistance to imatinib and entered second-line treatment. However, due to intolerance, they entered third-line treatment.

Abbreviations: IQR, interquartile range; TKI, tyrosine kinase inhibitor; ELTS, EUTOS long term survival; 1G, first-generation; 2G, second-generation; MR, molecular response; MMR, major molecular response; DMR, deep molecular response.

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The documented distributions of the EUTOS long term survival (ELTS) score risk assessment indicated 89 patients (64.5%) as low-risk in 1L, 35 patients (55.6%) as low-risk in 2L, and 30 patients (69.8%) as low-risk in the ≥3L cohorts. Prior TKI therapy predominantly involved imatinib in the 2L cohort (74.6%), while dasatinib was the main treatment in the ≥3L cohort (79.1%). The primary reason for therapy change was imatinib resistance, affecting 61.9% of 2L patients. Among the ≥3L patients, 83.7% exhibited resistance to both first-generation and second-generation TKIs. Baseline molecular responses in the 2L cohort revealed that 34.9% of patients achieved a response of less than MR1, while 31.7% reached the MR2-MMR response. In the ≥3L cohort, 48.9% of patients achieved the MR2-MMR response. During flumatinib treatment, five female patients experienced pregnancy. Among these, three patients were already in MMR at the time of unplanned conception. One patient met the criteria for treatment-free remission (TFR). Thus, therapy was discontinued and close monitoring with pregnancy management was initiated. Three patients have reinitiated flumatinib therapy after completing delivery, while one patient maintains MMR under observation. Additionally, one patient experienced unplanned pregnancy four months post-diagnosis when *BCR::ABL1* transcript levels were elevated. The patient prioritized disease control by opting for pregnancy termination followed by continued TKI therapy. This patient has now achieved TFR criteria and ceased therapy in November 2025 for planned conception.

Treatment Response in First-Line Flumatinib Cohort

Among the 138 patients with chronic myeloid leukemia in CML-CP receiving first-line flumatinib therapy, cytogenetic and molecular responses were observed as follows: the CCyR rates were 75.4% at 3 months and 81.2% at 6 months. The MMR was achieved by 50.7% of evaluable patients at 6 months and 66.7% at 12 months. Additionally, the DMR rates were 20.3% at 6 months and 35.5% at 12 months. The median times to CCyR, MMR, and DMR were 3.07 months (IQR 2.83–3.70), 6.01 months (IQR 3.10–9.16), and 8.83 months (IQR 5.65–16.92), respectively (Table 2). In addition, we compared clinical response (flumatinib vs DASISION vs ENESTnd) in Supplementary Figure 1.

Treatment Efficacy in Later-Line Cohorts

In a cohort of 106 patients with CML-CP undergoing flumatinib treatment as second-line or third-line and above, analyses of molecular responses stratified by baseline status indicated that patients with baseline MR2 achieved a DMR rate of 42.9% (27/63) following flumatinib therapy. In contrast, those without baseline MR2 had a DMR rate of 23.3% (10/43). Among patients who achieved MMR at baseline, the DMR rate was 63.6% (14/22), while it was significantly lower at 27.4% (23/84) for those who did not achieve MMR at baseline. Furthermore, 31.6% (31/98) of patients who did not achieve DMR at baseline subsequently reached DMR after flumatinib treatment. When analyzed by treatment line, all patients in subsequent lines achieved 100% maintenance of clinical response. Significant differences were observed between the 2L and ≥3L cohorts among patients without baseline MR2, MMR, and DMR (2L vs ≥3L: MR2, 78.6% vs 40.0%, p=0.011; MMR, 64.6% vs 33.3%, p=0.005; DMR, 42.1% vs 17.1%, p=0.009). In analyzing patients with last TKI resistance, significant differences were found between those lacking baseline MR2, MMR, and DMR when comparing

Table 2 Response During First-Line Flumatinib Treatment

Variables	N=138
CCyR by 3 months, N (%)	104 (75.4)
CCyR by 6 months, N (%)	112 (81.2)
MMR by 6 months, N (%)	70 (50.7)
MMR by 1 years, N (%)	92 (66.7)
DMR by 6 months, N (%)	28 (20.3)
DMR by 1 years, N (%)	49 (35.5)
Time to achieved CCyR, month, median (IQR)	3.07 (2.83–3.70)
Time to achieved MMR, month, median (IQR)	6.01 (3.10–9.16)
Time to achieved DMR, month, median (IQR)	8.83 (5.65–16.92)

Abbreviations: CCyR, complete cytogenetic response; MMR, major molecular response; DMR, deep molecular response; IQR, interquartile range.

imatinib-resistant patients to those resistant to both 1G and 2G TKIs (1G vs 1G/2G resistant: MR2, 78.3% vs 50.0%, p=0.052; MMR, 71.1% vs 34.8%, p=0.001; DMR, 43.9% vs 18.4%, p=0.008). However, subgroup analyses based on prior TKI responses did not reveal significant differences in therapeutic responses between the treatment warning and the resistance group following flumatinib therapy (Table 3). Among the four patients who developed ABL kinase domain mutations (E459K, N=1; F317L, N=3) during first-line therapy. The patient with the E459K mutation achieved a DMR at 16.7 months following a switch to flumatinib. Of the three patients with the F317L mutation, two reached DMR at 7.5 and 12.1 months, respectively, while one patient attained a CCyR at the last follow-up after 6.3 months of flumatinib treatment. During flumatinib therapy, eight patients experienced failure due to acquired resistance mutations. Among the three patients with the T315I mutation who were switched to olverembatinib, one achieved DMR, one achieved MMR, and one maintained complete hematologic response without improvement in molecular response. Among the four patients with the Y253H mutation who switched to dasatinib, two achieved MMR, while the other two subsequently failed dasatinib and were switched to olverembatinib. Additionally, one E255K patient who switched to dasatinib achieved CCyR. Importantly, no disease progression events were reported throughout the study period.

Low-Dose Therapy and TFR

Forty-seven patients (19.3% of the cohort) received reduced-dose flumatinib, with a mean treatment duration prior to dose reduction of 2.74 ± 2.79 years. The cohort consisted of 28 patients (59.6%) in 1L, 10 patients (21.3%) in 2L, and 9 patients (19.1%) in 3L therapy. The primary reasons for dose reduction were toxicity (48.9%, N=23), preparation for treatment discontinuation (36.2%, N=17), and economic factors (14.9%, N=7). At the time of dose reduction, clinical responses were recorded as follows: CCyR in 6 patients (12.8%), MMR in 5 patients (10.6%), and DMR in 36 patients (76.6%). Following the dose reduction, 41 patients (87.2%) were dosed at 400 mg/day, while 6 patients (12.8%) were dosed at 200 mg/day. During the dose reduction period, response loss was minimal, with 2 patients (4.3%) losing MMR and 1 patient (2.1%) losing DMR. Notably, among the seven first-line patients who were reduced to 400 mg within one month due to intolerance, 4 subsequently achieved DMR, 2 achieved MMR, and 1 maintained CCyR at the last assessment (Table 4). Among the eight patients who discontinued flumatinib, the median treatment duration was 4.61 years (IQR 3.56–5.07 years), with a median duration of DMR of 3.89 years (IQR 3.53–4.20). Reasons for discontinuation included pursuit of TFR (N=4), adverse events (N=2), and planned pregnancy (N=2). All three patients who relapsed resumed treatment with flumatinib, with

Table 3 Response During Later-Line Flumatinib Treatment

Response	MR2		MMR		DMR	
	With N (%)	Without N (%)	With N (%)	Without N (%)	With N (%)	Without N (%)
Baseline	63	43	22	84	8	98
Best response	27/63 (42.9)	10/43 (23.3)	14/22 (63.6)	23/84 (27.4)	6/8 (75.0)	31/98 (31.6)
Flumatinib treatment line						
2L, N=63	35/35 (100)	22/28 (78.6)	15/15 (100)	31/48 (64.6)	6/6 (100)	24/57 (42.1)
3L or above, N=43	28/28 (100)	6/15 (40.0)	7/7 (100)	12/36 (33.3)	2/2 (100)	7/41 (17.1)
p.value	–	0.011	–	0.005	–	0.009
Resistance to prior TKI[a]						
Resistant to imatinib, N=42	19/19 (100)	18/23 (78.3)	4/4 (100)	27/38 (71.1)	1/1 (100)	18/41 (43.9)
Resistant to 1G and 2G TKI, N=49	29/29 (100)	10/20 (50.0)	3/3 (100)	16/46 (34.8)	–	9/49 (18.4)
p.value	–	0.052	–	0.001	–	0.008
Response to last TKI						
Optimal, N=22	22/22 (100)	–	22/22 (100)	–	8/8 (100)	8/14 (57.1)
Warning, N=56	41/41 (100)	9/15 (60.0)	–	29/56 (51.8)	–	14/56 (25.0)
Failure, N=28	–	19/29 (65.5)	–	14/28 (50.0)	–	9/28 (32.1)
p.value	–	0.718	–	0.877	–	0.069

Notes: [a] 15 patients due to intolerance, but the clinical response is favorable.

Abbreviations: MR2, 2-log molecular response; DMR, deep molecular response; MMR, major molecular response; 2L, second line; 3L, third line; TKI, tyrosine kinase inhibitor; 1G, first-generation; 2G, second-generation.

Table 4 Dose Adjustment Strategy for Flumatinib

Low-dose flumatinib therapy, N = 47 (19.3%)	
Duration of flumatinib therapy before reduction dose, years, mean±SD	2.74±2.79
Treatment line	
1st line[a]	28 (59.6)
2nd line	10 (21.3)
3rd line	9 (19.1)
Reasons for reducing imatinib doses	
Toxicity	23 (48.9)
Preparation before discontinuation	17 (36.2)
Economic reasons	7 (14.9)
Clinical response before reduction dose	
CCyR	6 (12.8)
MMR	5 (10.6)
MR4 or better	36 (76.6)
Current dose	
400 mg/day	41 (87.2)
200 mg/day	6 (12.8)
Current status	
Loss of MMR	2 (4.3)
Loss of DMR	1 (2.1)
Discontinued flumatinib treatment, N=8	
Duration of treatment before discontinuation, year, median (IQR)	4.61 (3.56–5.07)
Duration of DMR before discontinuation, year, median (IQR)	3.89 (3.53–4.20)
Reason for discontinuation	
TFR pursuit	4 (50.0)
Adverse events	2 (25.0)
Pregnancy	2 (25.0)
Resumed TKIs[b]	
400mg qd	3 (37.5)

Notes: [a] 7 patients have reduced their dosage to 400mg due to intolerance during the one-month period of first-line treatment with flumatinib. Currently, four patients have achieved DMR, two patients have achieved MMR, and one patient achieved CCyR. [b] 2 patients achieved DMR after restarting 3 months treatment, and 1 patient achieved MMR after 1 months treatment.

Abbreviations: CCyR, complete cytogenetic response; MMR, major molecular response; DMR, deep molecular response; TKI, tyrosine kinase inhibitor; TFR, treatment-free remission; SD, standard deviation; IQR, interquartile range.

a dosage of 400 mg/daily, resulting in restored molecular responses. Specifically, two patients achieved DMR after three months of treatment, while one patient reached MMR after one month of treatment.

Safety Profile of Flumatinib

Among 244 CML-CP patients treated with flumatinib, most AEs of any grade occurred with the following frequency (Table 5): diarrhea (27.0%, 66/244), fatigue (12.3%, 30/244), and thrombocytopenia (11.5%, 28/244). Grade 3/4 AEs included diarrhea (2.9%, 7/244), thrombocytopenia (1.6%, 4/244), and neutropenia (0.4%, 1/244), hepatobiliary dysfunction (0.4%, 1/244), and rash (0.4%, 1/244).

Discussion

Flumatinib demonstrates a favorable safety profile, exhibiting AEs distinct from those of other 2G-TKIs. Hematological AEs include notable thrombocytopenia, with an overall incidence of 11.1% and 1.6% for grades 3–4, making it the primary reason for dose reduction or discontinuation of flumatinib, consistent with findings from prior phase III clinical trials.[12] The most frequently reported non-hematological AEs were diarrhea (26.6%) and fatigue (12.3%). The incidence of AEs during flumatinib treatment was lower than that observed in the FESTnd trial,[12] which may partly result from the retrospective

Table 5 Adverse Events on Flumatinib Therapy

Adverse Events	Dasatinib 100mg qd, N(%)[a]		Nilotinib 300mg bid, N(%)[a]		Flumatinib, N(%)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Leukopenia	–	–	–	–	13(5.3)	0
Neutropenia	–	61(24)	–	33(12)	13(5.3)	1(0.4)
Anemia	–	29(11)	–	10(4)	16(6.6)	0
Thrombocytopenia	–	50(19)	–	29(10)	28(11.5)	6(2.5)
Diarrhea	50(19%)	1(<1)	54(19.4)	3(1.1)	66(27.0)	7(2.9)
Nausea and vomiting	13-26[b] (5–10%)	0	42–62[c](15.1–22.2)	0–6(2.2)	21(8.6)	0
Gastrointestinal discomfort	–	–	–	–	16(6.6)	0
Constipation	–	–	56(20.1)	2(0.7)	12(4.9)	0
Musculoskeletal pain	57(22)	0	34(12.2)	0	16(6.6)	0
Rash	29(11)	0	107(38.4)	2(0.7)	22(9.0)	1(0.4)
Fatigue	22(9)	1(<1)	113(41)	–	30(12.3)	0
Hepatobiliary dysfunction	–	5 (1.9)[d]	4(1)	26(9)[e]	18(7.4)	1(0.4)
Elevated creatinine	–	3 (1)	–	–	16(6.6)	0
Pleural effusion	37(14)	2(1)	5(1.8)	2(0.7)	0	0
Symptomatic QT prolongation	–	–	4(1)	0	–	–

Notes: [a] Because the median duration of first-line flumatinib treatment was 2.48 years in our study, we preferred to compare the 2-year follow-up results of dasatinib (DASISION) and nilotinib (ENESTnd, 300mg bid). If the relevant adverse events were not recorded, we would choose the 3-year and 5-year follow-up data. [b] Nausea: 26(10); vomiting: 13(5). [c] Nausea: 62(22.2); vomiting: 42(15.1), no Grade 3–4 vomiting recorded. [d] Hepatobiliary dysfunction=elevated alanine aminotransferase (1) + elevated aspartate aminotransferase (1)+ Elevated total bilirubin (3). [e] Hepatobiliary dysfunction=aspartate aminotransferase increased (4) + alanine aminotransferase increased (12) + bilirubin (total) increased (10).

design of this study, potentially leading to underreporting of flumatinib-related AEs. Overall, flumatinib was associated with a significantly lower occurrence of AEs such as edema, limb pain, rash, neutropenia, and anemia. Most diarrhea cases were transient, manageable, and did not necessitate treatment interruption. Previous studies have indicated that long-term use of bosutinib[15] or imatinib[16] may lead to a decline in renal function. In this retrospective study, 15 patients (6.1%) exhibited elevations in creatinine, with eight having concomitant conditions such as hypertension and hyperuricemia that could exacerbate renal impairment. However, none discontinued flumatinib as a result. Further investigation is warranted to evaluate the long-term effects of flumatinib on renal function deterioration. Furthermore, our study demonstrates significantly lower incidences of grade ≥3 hematologic AEs, pleural effusion, and cardiovascular events in the flumatinib cohort compared to those reported in the DASISION and ENESTnd trials. Although inherent limitations exist in real-world evidence (including differential monitoring intensity and under-reporting bias), and no head-to-head randomized comparisons are available, flumatinib exhibits a favorably safety profile in real-world clinical practice.

Previous studies, including ENESTnd,[6] DASISION,[9] and FESTnd,[12] have found that patients treated with 2G-TKIs demonstrate higher rates of cytogenetic and molecular responses, as well as lower disease progression rates, particularly among the intermediate to high-risk subgroup defined by the Sokal score. However, these findings have not resulted in significant improvements in progression-free survival or overall survival.[17] Our analysis of 244 patients stratified by treatment line indicated that the 6-month and 12-month MMR and DMR rates for first-line flumatinib are substantially higher than those reported in the FESTnd trial (MMR: 50.7% vs 33.7% and 66.7% vs 52.6%; DMR: 20.3% vs 8.7% and 35.5% vs 23%). These findings are in line with recent studies on flumatinib[18,19] and suggest an increasing understanding of TKI treatment strategies, which contribute to improved molecular efficacy in patients. In comparison to historical data from nilotinib (ENESTnd) and dasatinib (DASISION), flumatinib also induced earlier and deeper molecular responses, as supported by comparative data on molecular responses and safety endpoints. These differential outcomes may be partially attributed to variations in baseline population characteristics (inclusion/exclusion criteria), adjusted *BCR::ABL1* monitoring frequencies and assessment schedules, and real-world attrition bias resulting from early treatment switching among suboptimal responders. Importantly, flumatinib exhibited a superior safety profile, particularly regarding its reduced risk of significant non-hematologic toxicities, such as severe QTc prolongation and pleural effusion. This enhanced safety significantly decreased treatment discontinuation

and dose reduction rates due to AEs during the initial phase, thereby improving treatment persistence and cumulative drug exposure. Sustained potent inhibition facilitated deeper early molecular responses.

The optimized clinical profile of flumatinib can be attributed to its molecular design. As a structurally refined second-generation *BCR::ABL1* TKI, flumatinib mesylate incorporates trifluoromethyl and pyridine moieties onto the imatinib scaffold. This strategic modification enhances binding affinity within the ABL kinase ATP pocket by strengthening hydrophobic interactions with key residues (eg, I293, L298, L354, V379), yielding approximately 30-fold greater in vitro potency than imatinib.[20] Flumatinib maintains activity against a broad spectrum of imatinib-resistant mutations (excluding T315I gatekeeper mutations), exhibiting submicromolar efficacy against variants such as V299L, F317L/I, and M351T.[21] Although flumatinib also inhibits PDGFR and c-KIT, its selectivity surpasses that of nilotinib and dasatinib, potentially accounting for its lower incidence of off-target toxicities, including pleural effusion and vascular events. Notably, flumatinib does not inhibit SRC-family kinases, a key mechanistic distinction from dasatinib, which may contribute to its reduced hemorrhagic risk.

In later lines of therapy, our results demonstrated that the efficacy of flumatinib is significantly affected by baseline molecular status. Patients who achieved a MMR prior to switching therapies exhibited a DMRrate of 63.6% following flumatinib treatment, whereas those without baseline MMR had only a 27.4% DMR rate ($P<0.001$). This finding emphasizes that the depth of early response is a critical determinant for successful treatment escalation, consistent with the results reported by Yang et al,[22] reinforcing the robustness and broader relevance of the conclusion that flumatinib demonstrates favorable clinical outcomes in later-line treatment settings. Additionally, flumatinib exhibited superior efficacy in imatinib-resistant patients, achieving a DMR rate of 42.1% in the 2L of treatment, compared to only 17.1% in cases of multiple TKI resistance (≥3L, $P=0.009$). This suggests that flumatinib may serve as a preferable rescue option before the onset of resistance to 2G-TKIs. Notably, in patients who were resistant to both 1G and 2G-TKIs, flumatinib induced MMR in 34.8% of those without baseline DMR and achieved DMR in 18.4% of baseline non-DMR patients, underscoring its potential to overcome prior TKI resistance.

Dose reduction strategies, implemented in 19.3% of patients, have proven feasible without compromising efficacy. Among those receiving a reduced dose of flumatinib, 76.6% achieved a DMR at the time of dosage adjustment, and 87.2% maintained a molecular response after the reduction. Notably, during the one-month period of first-line treatment with flumatinib, seven patients had their doses decreased to 400 mg due to intolerance. Currently, four of these patients have achieved DMR, two have attained a MMR, and one has reached a CCyR. This flexibility is of significant clinical importance, as it facilitates the management of toxicity while preserving treatment effectiveness. In recent years, TFR has become a new objective in the management of patients with CML,[23] faster DMR may translate into benefits for TFR. Eight patients subsequently attempted treatment cessation, with five maintaining TFR. These collective findings suggest that optimized dosing preserves efficacy while mitigating toxicity, thus enhancing the potential for TFR and significantly enriching the clinical practice landscape of flumatinib.

This study has several limitations. First, the retrospective design is vulnerable to selection and information bias, which prevents the establishment of causal relationships. Second, the single-center approach and small sample size restrict the generalizability of the findings. Third, the evaluation of AEs primarily depends on patient self-reports, which may lead to underreporting and an overestimation of safety. Finally, the short follow-up period limits the ability to assess long-term efficacy and cardiovascular AEs. To address these limitations, future research should focus on prospective, multi-center, large-sample registry studies with standardized inclusion and exclusion criteria and follow-up protocols. Furthermore, incorporating patient-reported outcomes and active monitoring mechanisms, as well as extending the follow-up duration, will enhance the validation of the study's conclusions regarding robustness and long-term safety.

Conclusions

This study demonstrates that flumatinib achieves significant clinical efficacy with a favorable safety profile in both first-line and later-line settings, offering expanded therapeutic options for Chinese CML patients. Furthermore, it validates the clinical viability of patient-tailored flumatinib dosing regimens and TFR strategies, thereby establishing an evidence-based framework for individualized therapeutic management in clinical practice. Future prospective studies are needed to further elucidate its role concerning TFR eligibility.

Abbreviations

CML, Chronic myeloid leukemia; CP, Chronic-phase; AEs, Adverse events; 1L, First-line; 2L, Second-line; 3L, Third-line; CCyR, Complete cytogenetic response; MMR, Major molecular response; DMR, Deep molecular response; MR, Molecular response; TKI, Tyrosine kinase inhibitors; 1G, First-generation; 2G, Second-generation; ELN, European LeukemiaNet; IQR, Interquartile ranges; ELTS, EUTOS long term survival; TFR, Treatment-free remissio; OTE, Off-target effects; EGFR, Epidermal Growth Factor Receptor; VEGFR, Vascular Endothelial Growth Factor Receptor; HER2, Human Epidermal Growth Factor Receptor 2; PDGFR, Platelet-Derived Growth Factor Receptor.

Data Sharing Statement

All data relevant to the study are included in the article or uploaded as Supplementary Materials.

Ethics Approval and Consent to Participate

This study has been approved by the institutional ethics committee of Tongji Medical College, Huazhong University of Science and Technology (Wuhan, China) ([2023] 0814). Informed consent was waived due to the retrospective nature of the study.

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Disclosure

The authors declare that there is no conflict of interest.

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