Safety and efficacy of flumatinib as later-line therapy in patients with chronic myeloid leukemia

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Abstract

The aim of this study was to evaluate the efficacy and safety of flumatinib in later-line treatment of Chinese patients with Philadelphia chromosome-positive chronic-phase chronic myeloid leukemia ((CP-CML) previously treated with tyrosine kinase inhibitors (TKI). Patients with CML-CP were evaluated for probabilities of responses, including complete hematologic response (CHR), cytogenetic response, and molecular response (MR), and adverse events after the later-line flumatinib therapy. Of 336 enrolled patients with a median age 50 years, the median duration of treatment with flumatinib was 11.04 months (range, 2-25.23). Patients who achieved clinical responses at baseline showed maintenance of CHR, complete cytogenetic response (CCyR) or 2-log molecular response (MR2), major molecular response (MMR), and 4-log molecular response or deep molecular response (MR4/DMR) in 100%, 98.9%, 98.6%, and 92.9% of patients, respectively. CHR, CCyR/MR2, MMR, and MR4/DMR were achieved in 86.4%, 52.7%, 49.6%, and 23.5% of patients, respectively, who lacked the respective clinical responses at baseline. The patients without response at baseline, treated with flumatinib as a second-line TKI, having no resistance to prior TKI or only resistance to imatinib, with response to last TKI, and with *BCR::ABL* ≤10% had higher CCyR/MR2, MMR, or MR4/DMR rates. The adverse events observed during the later-line flumatinib treatment were tolerable and consistent with those reported with the first-line therapy. Flumatinib was effective and safe in patients who were resistant or intolerant to other TKI. In particular, second-line flumatinib treatment induced high response rates and was more beneficial to patients without previous second-generation TKI resistance, thus serving as a probable treatment option for these patients.

Introduction

Tyrosine kinase inhibitors (TKI) have improved the outcome of patients with chronic-phase chronic myeloid leukemia (CML-CP) because of the higher response rate and lower risk of disease progression.[1,2] In one report, the relative survival of CML patients treated with TKI was 92%.[3] The current evidence suggests that, with appropriate follow-up, TKI therapy can be safely discontinued in patients who achieve a deep molecular response (DMR).[4]

The current paradigm for CML therapy has become sophisticated and complex, and includes the Food and Drug Administration-approved first-generation TKI imatinib; second-generation TKI, such as nilotinib, dasatinib, and bosutinib; and the third-generation TKI ponatinib and STAMP (specifically targeting the ABL myristoyl pocket) inhibitor, asciminib.[1,5,6] In frontline therapy for patients with CML-CP, ~50% of patients treated with imatinib and ~30% to 40% of patients treated with a second-generation TKI require a change of therapy within a span of 5 years because of resistance or intolerance.[7,8] Only ~30% to 55% of patients treated with TKI achieve a 4.5-log molecular response (MR4.5), enabling a discontinuation of TKI therapy.[9] Therefore, the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology and European LeukemiaNet (ELN) recommend the selection of first-line TKI (first- or second-generation) and subsequent TKI adjustments/switches on the basis of the risk level at initial diagnosis or follow-up, therapeutic goal, comorbidities, and milestone clinical response.[1,5]

Flumatinib mesylate, a second-generation TKI, is a derivative of imatinib and has greater selectivity and potency toward *BCR::ABL1* kinase compared with imatinib.[10] Flumatinib was approved by the National Medical Products Administration in late 2019 for patients with newly diagnosed CML-CP.[11] In real-world clinical practice, flumatinib has been used not only as first-line therapy but also as later-line therapy on the basis of its substantial inhibitory effect against *BCR::ABL* kinase and tolerable side-effect profile, but there are no data on its real-world efficacy and safety in a large population of patients.[12] In a recent phase III trial, flumatinib was reported to have higher efficacy and a lower rate of side effects than imatinib in patients with newly diagnosed CML-CP.[13] The rate of early molecular response (MR) at 3 months, the cumulative rate of major molecular response (MMR), and ≥4-log molecular response (MR4) or better were significantly higher in the flumatinib group than in the imatinib group.[13]

The special pyridine group and a trifluoromethyl group in flumatinib strongly interact with residues I293, L298, L354, and V379 in ABL kinase via hydrophobic interactions, causing an increase in potency of inhibition of *BCR::ABL1* kinase compared with imatinib and nilotinib. *In vitro* studies showed that flumatinib has a high potency against mutant *BCR::ABL1* kinases, such as V299L, F317L, F317I, and M351T mutations.[10,14,15] Furthermore, an unpublished phase Ia study of flumatinib in patients with advanced CML showed that flumatinib had considerable antileukemic activity and acceptable tolerability. The results indicated the potential therapeutic efficacy of flumatinib in patients who were resistant to other TKI.

The aim of this multicenter, retrospective, and observational study was, therefore, to analyze the efficacy and safety of flumatinib in the later-line setting in patients with CML who were resistant or intolerant to previous TKI in a real-world setting..

Methods

Study design and patients

This multicenter, retrospective, observational study included adult patients with CML, aged ≥18 years, who were treated with flumatinib as second- to fourth-line therapy between January 1, 2020 and January 21, 2022 in 18 centers in China. Patients who had received prior treatment with TKI such as imatinib, nilotinib, dasatinib, and flumatinib were included in this study. Patients treated with flumatinib were given other targeted drugs after the completion of the first-line flumatinib. After flumatinib was marketed, it was again used for treatment. As this is a real-world study, patients treated with all classes of TKI were included. All patients were diagnosed and confirmed as having Philadelphia chromosome-positive (Ph^+) CML using conventional cytogenetic assessment and/or *BCR::ABL1* transcript on the basis of quantitative or qualitative polymerase chain reaction at diagnosis. The disease phase was defined according to ELN 2020 recommendations.[1]

Treatment procedure

The reason for changing treatment to flumatinib was judged by the investigator and classified as resistance or intolerance to previous TKI. Flumatinib was initially prescribed at a dose of 600 mg/day for most patients; the dose could be modified by the clinician during treatment according to clinical practice.

Study endpoints

The primary outcome was to determine the probabilities of responses including complete hematologic response (CHR), cytogenetic response, and MR after the later line of flumatinib. The secondary outcome was to assess adverse events.

Response evaluation

The responses to treatment, including CHR, cytogenetic response, and MR, were judged by the investigator according to ELN 2020 response criteria.[1] Quantitative detection of *BCR::ABL1* transcript was performed in the laboratory using a certified international scale (IS). Responses of MR4

or better are referred to as DMR in this study. Mutation analysis of the *ABL1* kinase domain was performed optionally on the basis of the decision of the investigators. A complete cytogenetic response (CCyR)/2-log molecular response (MR2) was defined as no Ph^+ chromosome in ≥20 metaphases by conventional G-banding of chromosomes or *BCR::ABL1* transcript ≤1% on the IS. Adverse events were graded in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

Ethical considerations

The study was approved by the Ethics Committee of the Blood Diseases Hospital, Chinese Academy of Medical Sciences (ethics number: QTJC2021008-EC-1). The trial was conducted in accordance with the protocol and the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. This is a retrospective study, and informed consent from patients was waived.

Statistical analysis

Quantitative variables are expressed as median and range, whereas qualitative variables are expressed as number and percentage. Time-to-event variables, such as survival and cumulative rate of response, were estimated by the Kaplan-Meier method. The difference in time-to-event variables between groups was analyzed using the log-rank test. All statistical analyses were performed using SPSS version 21 (IBM Corporation, NY, USA).

Results

Patients' disposition and baseline clinical characteristics

Of 336 patients with CML included in this retrospective study, 190 (56.5%) males and 146 (43.4%) females with a median age of 50 years (range, 18-87) received flumatinib as second- or later-line treatment. The median time from enrollment to last follow-up was 11.4 months (range, 2-25.46). The detailed disposition of the patients is shown in *Online Supplementary Figure S1*. At diagnosis, only three patients had accelerated phase disease, whereas the remaining 333 patients had chronic phase CML All patients in the chronic phase received flumatinib treatment. Seven patients received 200 mg of flumatinib and 28 patients received 400 mg of flumatinib, as once-daily doses. All other patients were treated with higher flumatinib doses (600 mg once daily), with a median dosage of 600 mg/day. The treatment was switched from the previous TKI to flumatinib because of intolerance, non-optimal response, or to achieve a better response.

Five patients entered the first-line phase III clinical study of flumatinib compared with imatinib. After the experiment had been designed, flumatinib became unavailable on the market and, hence, its administration was stopped and it was replaced by other TKI (imatinib in 4 cases and nilotinib in 1 case). Treatment with imatinib or nilotinib was found to be effective in all five patients who had optimal responses even in the absence of treatment with flumatinib. After the launch of flumatinib, the five patients were switched to flumatinib treatment again: three treated with imatinib were switched to flumatinib because of edema; one patient who maintained MR4 during imatinib treatment was changed to flumatinib in pursuit of a deeper MR; and the patient treated with nilotinib was changed to flumatinib again because of economic reasons. Of note, none of the five patients developed adverse events while taking flumatinib again.

The baseline clinical characteristics of the patients are presented in Table 1. Among the total patients, 220 patients had European Treatment and Outcome Study for CML (EUTOS) long-term survival (ELTS) information, with 139 (63.2%), 49 (22.3%), and 32 (14.5%) patients being in low, intermediate, and high ELTS-risk groups, respectively (Table 1). Among the 336 patients treated with flumatinib, *ABL* mutations were tested in 291 patients before initiating flumatinib: 14 (4.8%) patients had *ABL* mutations with one patient each showing E255K, V260A, E279K, M351T, Y253F, M351T/F359I, and Y253H/F317L double mutations; two patients each had Y253H and E459K mutations; and three patients had an F317L mutation. Among the patients receiving flumatinib treatment, 199 (58.9%) received flumatinib as a second-line TKI, while 100 (29.8%) and 37 (11%) patients received flumatinib as the third- and fourth-line TKI, respectively. The first-line TKI was imatinib in 288 (85.7%) patients, whereas 31, 12, and five patients received nilotinib, dasatinib, and flumatinib, respectively, as first-line treatment. In total, 171 (50.9%) patients were not resistant to prior TKI, whereas 97 (28.9%), 24 (7.1%), and 44 (13.1%) patients were resistant to imatinib, a second-generation TKI, and both imatinib and a second-generation TKI, respectively. There were 121 (36%) and 90 (26.8%) patients with no response and a warning response to the last prior TKI during the initiation of flumatinib treatment, respectively (Table 1).

In a total of 110 patients, different comorbidities were reported at baseline. The major comorbidities were hypertension (N=27), diabetes mellitus (N=18), coronary heart disease (N=14), and cardiovascular or cerebrovascular embolic diseases (N=7).

Efficacy

The median duration of flumatinib treatment was 11.04 months (range, 2-25.23) in the overall population. The reasons for treatment discontinuation included treatment failure (N=13), disease progression (N=4), intolerance (N=8), high cost (N=4), suboptimal response (N=6), loss of previous DMR (N=2), and non-CML death (N=1).

The cumulative response during flumatinib treatment is shown in Figure 1 and Table 2. The patients without evaluable data were considered without response. CHR and MR

were not reported in three and four patients, respectively, during the flumatinib treatment because of lack of data. In most patients with a baseline response, efficacy was maintained after flumatinib treatment. CHR was achieved in 38 (86.4%) patients without CHR at baseline after flumatinib therapy, three patients did not achieve CHR, and three patients were not eligible for CHR evaluation. After a median time of 9 months, 79 (52.7%) patients without CCyR/MR2 at baseline had achieved CCyR/MR2 following flumatinib therapy. Out of 262 patients without MMR at baseline, 130 (49.6%) patients had achieved MMR at a median of 11.3 months of flumatinib therapy and four patients were ineligible for MMR evaluation. DMR was achieved in 69 (23.5%) patients without DMR at baseline after flumatinib therapy (Table 2).

BCR::ABL1 transcript levels were detected in 322 patients after exposure to flumatinib for 3 months. Among 110/322 patients with transcript levels >10% at baseline, 75 patients achieved an early MR of $BCR::ABL1^{IS}$ ≤10%.

Subgroup analysis

The probabilities of response from CHR to MR after later-line flumatinib therapy were analyzed on the basis of clinical parameters which showed an association of flumatinib response with treatment lines, resistance to prior TKI, response to the last administered TKI and their transcript expression levels, and mutation status at baseline (Table 2). In patients without CHR at baseline, second-, third- and fourth-line flumatinib therapy induced CHR at similar rates. With higher lines of flumatinib treatment, cytogenetic response or MR was reduced and the median time to obtain these responses increased. (Table 2, *Online Supplementary Figure S2*). CCyR/MR2 was achieved after a median time of 6.2 and 12 months of second- and third-line flumatinib

Table 1. Baseline characteristics of patients treated with flumatinib according to line of treatment.

Characteristics	2nd line N=199	3rd line N=100	4th line N=37	Total N=336
Male, N (%)	117 (58.8)	55 (55)	18 (48.6)	190 (56.5)
Age in years, median (range)	52 (18-87)	47 (21-79)	48 (25-77)	50 (18-87)
Time from diagnosis to flumatinib treatment in months, median (range)	15 (0.4-375.3)	50.6 (3-246)	104.9 (9-461.8)	32 (0.4-461.8)
Time from first TKI to flumatinib in months, median (range)	14.5 (0.4-185.3)	45.7 (3-163.6)	71.5 (9.2-197.8)	29.5 (0.4-197.8)
ELTS group, N (%) ELTS low ELTS intermediate ELTS high	N=150 97 (64.7) 35 (23.3) 18 (12)	N=56 34 (60.7) 12 (21.4) 10 (17.9)	N=14 8 (57.1) 2 (14.3) 4 (28.6)	N=220 139 (63.2) 49 (22.3) 32 (14.5)
Prior TKI, N Imatinib Dasatinib Nilotinib Flumatinib Bosutinib	 165 9 25 0 0	 97 72 26 5 0	 36 35 34 - 1	 198 116 85 5 1
Resistant to prior TKI, N (%) Imatinib 2G TKI 1G and 2G TKI	 68 (34.2) 15 (7.5) 0	 25 (25) 6 (6) 21 (21)	 4 (10.8) 3 (8.1) 23 (62.2)	 97 (28.9) 24 (7.1) 44 (13.1)
Response to last TKI, N (%) Failure Warning	 80 (40.2) 49 (24.6)	 21 (21) 32 (32)	 20 (54.1) 9 (24.3)	 121 (36) 90 (26.8)
Response at baseline, N (%) CHR MR1 MR2 MMR MR4 or DMR	 172 (86.4) 114 (57.3) 96 (48.2) 34 (17.1) 20 (10.1)	 89 (89) 78 (78) 73 (73) 32 (32) 17 (17)	 31 (83.8) 20 (54.1) 17 (45.9) 8 (21.6) 5 (13.5)	 292 (86.9) 212 (63.1) 186 (55.4) 74 (22.0) 42 (12.5)

N: number; TKI: tyrosine kinase inhibitor: ELTS: European Treatment and Outcome Study for chronic myeloid leukemia long-term survival; 2G: second generation; 1G: first generation; CHR: complete hematologic response; MR1: 1-log molecular response; MR2: 2-log molecular response; MMR: major molecular response; DMR: deep molecular response.

Table 2. Response during flumatinib treatment.

Response	CHR		CCyR/MR2		MMR		MR4 or better (DMR)	
	With N (%)	Without N (%)	With N (%)	Without N (%)	With N (%)	Without N (%)	With N (%)	Without N (%)
Baseline	292	44	186	150	74	262	42	294
Best response	292/292 (100)	38/44 (86.4)	184/186 (98.9)	79/150 (52.7)	73/74 (98.6)	130/262 (49.6)	39/42 (92.9)	69/294 (23.5)
Flumatinib treatment line								
2L, N=199	172/172 (100)	22/27 (81.5)	94/96 (97.9)	63/103 (61.2)	34/34 (100)	93/165 (56.4)	19/20 (95)	50/179 (27.9)
3L, N=100	89/89 (100)	10/11 (90.9)	73/73 (100)	12/27 (44.4)	32/32 (100)	29/68 (42.6)	17/17 (100)	18/83 (21.7)
4L, N=37	31/31 (100)	6/6 (100)	17/17 (100)	4/20 (20)	7/8 (87.5)	8/29 (27.6)	3/5 (60)	1/32 (3.1)
P	0.058	0.488	0.376	0.000	0.261	0.000	0.376	0.000
Resistance to prior TKI								
Not resistant, N=171	162/162 (100)	9/9 (100)	134/135 (99.3)	28/36 (77.8)	62/62 (100)	71/109 (65.1)	34/36 (94.4)	39/135 (28.9)
Resistant to imatinib, N=97	80/80 (100)	13/17 (76.5)	36/36 (100)	34/61 (55.7)	11/11 (100)	43/86 (50)	5/5 (100)	27/92 (29.3)
Resistant to 2G TKI,* N=68	50/50 (100)	16/18 (88.9)	14/15 (93.3)	18/53 (32.1)	0/1	16/67 (23.9)	0/1	3/67 (4.5)
P	0.092	0.371	0.121	0.000	0.039	0.000	0.096	0.000
Response to last TKI								
Optimal, N=125	118/118 (100)	7/7 (100)	96/97 (99)	22/28 (78.6)	73/74 (98.6)	36/51 (70.6)	39/42 (92.9)	31/83 (37.3)
Warning, N=90	85/85 (100)	4/5 (80)	68/68 (100)	12/22 (54.5)	-	48/90 (53.3)	-	17/90 (18.9)
Failure, N=121	89/89 (100)	27/32 (84.4)	20/21 (95.2)	45/100 (45)	-	46/121 (38)	-	21/121 (17.4)
P	0.441	0.481	0.132	0.001	-	0.000	-	0.001
Baseline transcript level								
≤10%, N=213	211/211 (100)	2/2 (100)	173/174 (99.4)	27/39 (69.2)	73/74 (98.6)	80/139 (57.6)	39/42 (92.9)	42/171 (24.6)
>10%, N=123	81/81 (100)	36/42 (85.7)	11/12 (84.6)	52/111 (46.8)	-	50/123 (40.7)	-	27/123 (22)
P	0.318	0.004	0.148	0.005	-	0.004	-	0.446
Mutation status at baseline								
No mutation, N=277	246/246 (100)	25/31 (80.6)	157/157 (100)	71/120 (59.2)	64/65 (98.5)	115/211 (54.5)	35/37 (94.6)	65/240 (27.1)
Mutation, N=14	9/9 (100)	5/5 (100)	2/3 (66.7)	2/11 (18.2)	0/1	3/13 (23.1)	1/1 (100)	1/13 (7.7)
Total, N=291	255/255 (100)	30/36 (83.8)	159/160 (99.4)	73/131 (55.7)	64/66(97)	118/224 (52.7)	36/38 (94.7)	66/253 (26.1)
P	0.91	0.292	0.1	0.053	0.861	0.169	0.665	0.268

*Resistance to 2G TKI includes resistance to only a 2G TKI or resistance to both imatinib and a 2G TKI. CHR: complete hematologic response; CCyR/MR2: complete cytogenetic response/2-log molecular response; DMR: deep molecular response; MMR: major molecular response; MR4: 4-log molecular response; N: number; 2L: second line; 3L: third line; 4L: fourth line; TKI: tyrosine kinase inhibitor; 2G: second generation.

treatment, respectively. Similarly, the median time to achieve MMR was 6.9 and 16.9 months after second- and third-line flumatinib treatment, respectively. The median time was not reached for CCyR/MR2 and MMR in fourth-line treatment and for DMR in all groups.

The response to flumatinib therapy was also evaluated according to the patients' history of resistance to prior TKI, as presented in Table 2. Most of the patients without CHR at baseline achieved CHR after exposure to flumatinib irrespective of the status of resistance to prior TKI. Patients without CCyR/MR2 or MMR at baseline, those without previous resistance to prior TKI had higher CCyR/MR2 or MMR rates than those with simple imatinib resistance, whereas patients with resistance to second-generation TKI had the lowest CCyR/MR2 or MMR rates. In the baseline population without DMR, only 4.5% of patients resistant to second-generation TKI obtained DMR after flumatinib treatment. The rate of DMR was similar in patients with no previous resistance or resistant to imatinib only. The median time of attaining CCyR/MR2 in the patients with no resistance, those resistant to imatinib only, and those resistant to a second-generation TKI (only second-generation or imatinib and second-generation) was 3.8, 8.5, and 19.2 months, respectively, whereas the median time of attaining MMR in these patients was 6.2, 9.9, and 20.1 months, respectively (Table 2; *Online Supplementary Figure S3*).

We also analyzed the impact of the response to the last TKI before flumatinib on the subsequent efficacy of flumatinib treatment. According to the ELN 2020 criteria for second-line TKI therapy, patients were categorized into failure, warning, and optimal groups. Patients who had not reached efficacy evaluation endpoints but were given replacement flumatinib treatment because of adverse events or to achieve better efficacy were included in the optimal group. As detailed in Table 2, most patients with response at baseline maintained their CHR, CCyR/MR2, or MMR during the flumatinib therapy. The patients who had optimal responses to the last prior TKI had higher rates of CCyR/MR2, MMR, and DMR when compared to those in the warning or failure response groups. The patients with optimal response to the last prior TKI also had a shorter median time to corresponding responses. The median time to CCyR/MR2, MMR, and DMR was 3.8 months, 6 months, and 15 months in patients with optimal response; 8.1 months, 8.1 months, and not reached in patients in the warning response group; and 12 months, 19.2 months, and not reached in the failure group, respectively.

The *BCR::ABL* transcript levels also affected some efficacy parameters of flumatinib treatment. CHR at baseline was maintained in all 292 patients independent of baseline transcript levels during flumatinib treatment. With a median exposure of 11.04 months to flumatinib treatment, the patients with transcript levels ≤10% at baseline showed a higher probability of achieving CCyR/MR2 and MMR as compared with those with transcript levels >10%, whereas the probabilities of achieving DMR were similar in both groups

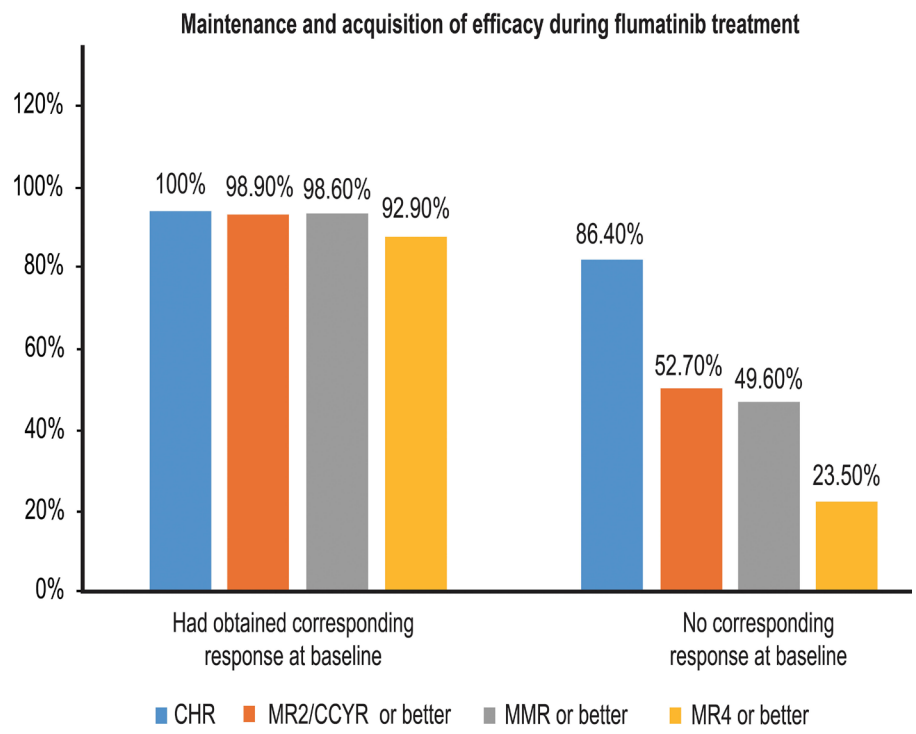

Figure 1. Hematologic, cytogenetic and molecular responses after flumatinib treatment. CHR: complete hematologic response; MR2/CCYR: 2-log molecular response/complete cytogenetic response; MMR: major molecular response; MR4: 4-log molecular response.

(Table 2; *Online Supplementary Figure S5*). There were 12 patients with CCyR confirmed using traditional chromosome G-banding having transcript levels >10% at baseline, of whom 11 maintained their CCyR during flumatinib therapy, whereas MMR and DMR were achieved in eight and four patients, respectively.

Fourteen patients had mutations at baseline and were treated with flumatinib. Of the four patients having mutations in Y253H/Fm, one patient had F317L co-mutation, two patients had discontinued flumatinib because of failure or progression at 5 and 9.9 months, and one patient had changed to flumatinib from dasatinib because of pleural effusion and maintained a DMR at the last follow-up with 8.9 months of flumatinib exposure. Although the patient with Y253H/F317L double mutation achieved a CHR, there was no further improvement during exposure to flumatinib for 15.2 months. The only patient with E255Km treated with flumatinib as second-line treatment maintained a CHR with no improvement in MR during flumatinib treatment for 6.7 months. The single patient with V260Am, who was resistant to nilotinib as well as without a CHR at baseline, changed to second-line flumatinib therapy for 6.2 months and achieved a CHR but without an early MR. The patient with E279Km and resistant to imatinib as well as without a CHR at baseline achieved a MMR within 7 months of flumatinib treatment. In total, three patients with F317Lm had a better response to flumatinib. Of these patients, one patient each achieved a MR4 and MMR. The patient with M315T/F359I co-mutation progressed to the accelerated phase after 6.7 months of flumatinib treatment. The patient with M351Tm received flumatinib for 4.5 months and achieved an early MR, whereas

two patients with E459Km received flumatinib for 4 months and maintained a CHR with stable *BCR::ABL* transcript levels. Multivariate analysis showed the predictive factors along with their association with the achievement of CCyR, MMR, and DMR during the later-line flumatinib therapy. Of these factors, the only independent factor was a history of resistance to prior TKI treatment (*Online Supplementary Table S1*).

Safety

Overall, 204 patients had multiple adverse events related to prior TKI at baseline, and most of these adverse events were mitigated after the flumatinib treatment. *Online Supplementary Table S2* shows changes in >5% adverse events during the last TKI before the flumatinib treatment. Among imatinib-related adverse events, only one patient each had sustained rash and itching, cytopenia, and gastrointestinal adverse events without improvement after flumatinib therapy. Of 13 patients with cytopenia on nilotinib treatment, only five patients still had cytopenia without any improvement during flumatinib therapy. Eight patients with abnormal liver function related to nilotinib fully recovered after initiating flumatinib treatment. Of nine patients with cardiac-related adverse events during nilotinib treatment, two patients did not fully recover after the initiation of flumatinib treatment. Only one patient with pleural effusion did not recover after the discontinuation of dasatinib and showed sustained pleural effusion because of lung metastases during flumatinib treatment, which was not a flumatinib-related adverse event. Among the 16 patients with cytopenia on dasatinib treatment, eight patients achieved complete remission and six patients had alleviated symptoms after flumatinib treatment.

The adverse events reported during flumatinib treatment are listed in Table 3. Of the total patients, there were 66 with hematologic toxicities. Among these patients, hematologic adverse events persisted in 23 patients from the last prior TKI before switching to flumatinib treatment, and 43 patients showed new adverse events after starting flumatinib treatment. Apart from one patient with atrial fibrillation who had cerebral infarction during third-line flumatinib treatment, no new cardio-cerebrovascular ischemic events were reported in this study.

Among all patients, eight patients discontinued the flumatinib therapy because of adverse events, including grade ≥2 cytopenia (N=5), grade 3 rash (N=1), grade 3 diarrhea (N=1), and leg pain (N=1). Apart from one patient with chronic heart failure at baseline who died of heart failure after flumatinib treatment, none of the patients with diverse complications had deterioration of comorbidities leading to the discontinuation of flumatinib therapy.

Table 3. Adverse events on flumatinib therapy.

Adverse events	All N=336	Grade 3-4 N=336
Hematologic, N (%)	66 (19.3)	-
Thrombocytopenia	52 (15.5)	23 (6.8)
Leukocytopenia	18 (5.4)	8 (2.4)
Anemia	28 (8.3)	5 (1.5)
Non-hematologic, N (%)		
Gastrointestinal	60 (17.86)	0 (0.0)
Diarrhea	41 (12.20)	3 (0.89)
Nausea	8 (2.38)	0 (0.0)
Vomiting	5 (1.49)	0 (0.0)
Constipation	4 (1.19)	0 (0.0)
Abdominal pain	2 (0.60)	0 (0.0)
Esophagitis	2 (0.60)	0 (0.0)
Rash	20 (6)	1 (0.3)
Pruritus	3 (0.89)	0 (0.0)
Skeletal muscle and joint pain	10 (2.98)	0 (0.0)
Headache and dizziness	5 (1.49)	0 (0.0)
Sub-acute thyroiditis	4 (1.19)	0 (0.0)
Hyperthyroidism	3 (0.89)	0 (0.0)
Arrhythmia	3 (0.89)	0 (0.0)
Facial edema	2 (0.60)	0 (0.0)
Paresthesia	2 (0.60)	0 (0.0)
Cerebral infarction	1 (0.30)	0 (0.0)
Fatigue	1 (0.30)	0 (0.0)
Menstrual disturbance	1 (0.30)	0 (0.0)
Peripheral neuritis	1 (0.30)	0 (0.0)
Liver enzymes elevation	7 (2.1)	0 (0.0)
Increased bilirubin	4 (1.19)	0 (0.0)
Creatinine elevation	18 (5.36)	0 (0.0)
Elevated uric acid	2 (0.6)	0 (0.0)

Discussion

To the best of our knowledge, this is the first and largest global post-market real-world study of flumatinib to date in patients with CML resistant or intolerant to other TKI. Previously published *in vitro* studies have reported an inhibitory action of flumatinib against both wild-type *ABL* and *ABL* with mutations.[15] However, there are limited studies on the use of flumatinib in patients with CML who are intolerant or resistant to other TKI.[10,13,14]

In this retrospective study, flumatinib showed a promising efficacy and safety profile when used as later-line therapy in patients with CML-CP. Indeed, flumatinib was effectively used as the second-, third- and fourth-line TKI in patients resistant/intolerant to ≥1 TKI, including imatinib, nilotinib, and/or dasatinib. A significant improvement was observed in CHR and MR in patients receiving flumatinib treatment. The CCyR/MR2, MMR, and DMR increased to 78.3%, 60.4%, and 32.1% from 55.4%, 22%, and 12.5% at baseline, respectively. The earlier the shift to flumatinib treatment, the higher the response. In addition, patients with no resistance to a prior TKI or simple imatinib resistance had a higher response to flumatinib therapy.

In the present study, only 5% of the tested patients had an *ABL* mutation. *In vitro* studies have shown that flumatinib has an inhibitory effect on some mutated *ABL*, but this has not been confirmed by clinical studies. In real-world patients with *ABL* mutations, clinicians should refer to ELN,

NCCN, or Chinese guidelines on recommended TKI, which do not include flumatinib. Therefore, more patients who are mutation-negative but resistant or intolerant to other TKI choose flumatinib as later-line treatment.

The CCyR/MR2, MMR, and DMR rates reported for later-line treatment in this study were comparable to those in previous studies. Studies of nilotinib, dasatinib, and bosutinib as second-line treatments for chronic phase patients who failed or were intolerant to imatinib therapy have found CCyR rates of 44% to 57% and MMR rates of 28% to 38%.[16-19] Corresponding values when these TKI were used as third-line treatment were 17.1% to 32.4% (CCyR) and 15% to 21.1% (MMR)[19-24] and the BYOND study found higher cytogenetic and MR rates with bosutinib in post-line treatment. Indeed, the phase IV BYOND study showed that the CCyR, MMR, and MR4 rates obtained by bosutinib in Ph^+ CML-CP patients with no TKI efficacy at baseline were 75%, 76%, and 64.9%, respectively, when the drug was used as second-line treatment, 68.4%, 64.3%, and 52.6% when used as third-line treatment and 47.1%, 38.5%, and 29.7% when used as a fourth-line TKI.[25]

In the present study, the rates of CCyR, MMR, and DMR to flumatinib were 61.2%, 56.4%, and 27.9%; 44.4%, 42.6%, and 21.7%; and 20%, 27.6%, and 3.1% when the drug was used as a second-, third-, and fourth-line treatment, respectively, in patients without response at baseline. For an accurate interpretation of difference of response rates achieved with flumatinib compared with other second-generation TKI in later-line treatment, as described above, the baseline characteristics were compared. We found that the major cytogenic response (*BCR::ABL* transcript ≤10%) rate at baseline was 63.1% in our study compared with 11%, 14% to 20%, and 77.8% observed in nilotinib, dasatinib, and BYOND studies, respectively. These data show that the CCyR and MR to flumatinib are comparable or non-inferior to other second-generation TKI as later-line treatment in patients with CML-CP.

Previous studies have shown that the use of other second-generation drugs as a back-line treatment after failure of second-generation drugs is not ideal, and the third-generation drugs ponatinib and STAMP show higher efficacy in patients after the failure of second-generation TKI.[6,26] Our study also showed that flumatinib has no obvious benefit for patients who failed other second-generation TKI. Since ponatinib and STAMP are not on the market in China, Chinese patients who have failed to benefit from second-generation TKI should consider switching to the third-generation olverembatinib.[27]

Adverse events observed in the current study included hematologic toxicity, diarrhea, elevated creatinine levels, and hepatic insufficiency, whereas the FESTnd trial documented the occurrence of hematologic adverse events, diarrhea, and elevated levels of liver enzymes. In the current study, eight patients discontinued flumatinib treatment because of intolerance, whereas in the FESTnd study, flumatinib treatment discontinuation was reported because of abnormalities in liver function, thrombocytopenia, and aminotransferase elevation in 10.2%, 3.5%, and 3.1% of patients, respectively.[13] The incidence of adverse events during flumatinib treatment was lower in this study than in the FESTnd trial, which could be partially because of the retrospective nature of this study, thereby causing underrepresentation of flumatinib-related adverse events. Although there was a lower incidence of flumatinib-related adverse events in this study, the safety profile of flumatinib was consistent with that found in the FESTnd study. An improvement in terms of incidence and severity of adverse events related to prior TKI was observed after switching to flumatinib treatment, which revealed no significant cross-intolerance between flumatinib and other TKI such as imatinib, nilotinib, or dasatinib.

According to the ELN 2020 guidelines, dasatinib is contraindicated in patients with respiratory failure and pleuropulmonary or pericardial disease because of the higher incidence of pulmonary toxicities.[1] The toxicity profile of flumatinib in the current study and FESTnd trial indicated that it would be safe for patients with pleuropulmonary disease. The frequent occurrence of glycolipid abnormalities was observed in patients treated with nilotinib or ponatinib, thereby leading to ischemic vascular events.[28] Therefore, a history of coronary heart disease, cerebrovascular accidents, or peripheral arterio-occlusive disease was recommended to be a strong contraindication, along with increased risk of vascular adverse events in patients with hypertension, hypercholesterolemia, and diabetes mellitus, by the ELN 2020 guidelines in patients treated with nilotinib.[1] No vascular events were reported during flumatinib therapy in either the present study or the FESTnd trial.[13] Although these findings suggest that flumatinib treatment does not increase the risk of vascular events, further validation may be warranted given the relatively short duration of the present study (median duration of treatment: 11.04 months).

Previous studies have reported a decline in renal function associated with long-term exposure to bosutinib or imatinib.[29,30] In this retrospective study, grade 1 increases in creatinine levels occurred in 18 (5.36%) patients, of whom five had comorbidities such as hypertension, hyperuricemia, or diabetes, thus increasing the possibility of kidney damage; none of these patients discontinued flumatinib. However, detailed studies are still required to evaluate the deterioration of renal function during prolonged flumatinib treatment.

The present study has a few limitations. As it was retrospective in nature, the grading of adverse events lacked accuracy, as they were evaluated on the basis of the improvements including reduced severity and complete relief after treatment with flumatinib or other TKI according to the clinical records.

In conclusion, flumatinib induces high rates of CCyR and MMR or DMR in CML-CP patients as a later-line treatment, especially in patients with no previous TKI failure or only imatinib failure. The incidence of adverse events during flumatinib treatment was tolerable and comparable with the

adverse events reported in the previous studies. Therefore, the present study showed that treatment with flumatinib in patients who were resistant or intolerant to prior TKI was reasonable.

Disclosures

No conflicts of interest to disclose.

Contributions

YY, YL, and HS curated data and conducted a formal analysis. LM, HL, CC, JH, XS, MD, YZ, DA, JingW, HZ, LH, QL, CZ, and LS curated data. WL, HZ, and BL curated data, conducted formal analyses, conceived the study, wrote the original draft of the manuscript, reviewed and edited it. JianW curated data and wrote, reviewed and edited the manuscript.

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Data-sharing statement

Data that support the results of this study are available from the corresponding author upon reasonable request.

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