Low-dose tyrosine kinase inhibitors in patients with chronic myeloid leukemia: a retrospective study in China

The advent of tyrosine kinase inhibitors (TKI) has significantly improved the treatment and prognosis of chronic myeloid leukemia (CML) patients who can nowadays expect a near-normal life expectancy.[1,2] However, the adverse events accompanying lifelong treatment dramatically diminish patients' quality of life and dependence on TKI, eventually leading to poor treatment outcomes.[3,4] In addition, long-term TKI treatment increases the financial burden of patients and society.[5] Several clinical studies have investigated the possibility of TKI discontinuation in patients with sustained deep molecular response (DMR). Only approximately 50% of patients with DMR remained in treatment-free remission (TFR) at least 1 year after discontinuing TKI.[6] In clinical practice, TKI dose reduction is an important measure for alleviating adverse events, improving quality of life, and adherence. Interestingly, Fassoni *et al.* developed a patient data-based mathematical model which showed that a reduction in TKI dose of at least 50% did not exacerbate long-term treatment outcomes.[7] Recent evidence suggests that low-dose TKI can effectively maintain molecular response without impairing the achievement of TFR.[8] Nonetheless, limited data are available on the effect of reduced TKI in China. In this multi-center, retrospective trial, we sought to ascertain whether dose reduction of TKI is appropriate for patients with discontinuation requirements, financial stress, and adverse effects.

We retrospectively analyzed the efficacy of TKI dose reduction of CML-CP patients from September 2011 to October 2021 from three hospitals in China (Union Hospital, Tongji Medical College, Huazhong University of Science and Technology; Huazhong University of Science and Technology Union Shenzhen Hospital (Nanshan Hospital); The Affiliated Cancer Hospital of Zhengzhou University). All included patients were 14 years of age or older, with positive BCR-ABL1 transcripts and no history of accelerated or blast phase. Patients who had previously received hematopoietic stem cell transplantation or immune cell therapy were excluded. In this study, we included 108 patients (54 females and 54 males, median age 43.5 years (range, 14-70 years) who underwent low-dose TKI treatment for financial burden (21.3%), attempt for TFR (23.1%), and adverse events (55.6%) (Table 1). TKI at dose reduction were imatinib (n=51), dasatinib (n=47), and nilotinib (n=10) (Figure 1). Patients were treated at doses of imatinib of 300 mg/d (n=2), 200 mg/d (n=48), and 400 mg every other day (qod) (n=1). Dasatinib at a dose of 50 mg/d (n=45), 70 mg/d (n=1), and 50 mg qod (n=1) was prescribed. The doses of nilotinib were 300 mg/d (n=1), 400 mg/d (n=9). 28 (25.9%) patients displayed resistance to at least one TKI before dose reduction according to European LeukemiaNet recommendations.[2] Ninety eight of 108 (90.7%) patients achieved major molecular remission (MMR) at the time of dose reduction with a median duration of 49.8 months (range, 1-146 months), among which 92 patients achieved MR4 (BCR-ABL IS≤0.01%) with a median duration of 39.8 months (range, 1-146 months). Ten non-MMR patients received low-dose TKI due to adverse events. Molecular relapse-free survival (MRFS) in MMR and MR4 were

Table 1. Patient characteristics.

Patient characteristics (N=108)	N (%)
Median age at diagnosis, years (range)	43.5 (14-70)
Female, sex	54 (50)
TKI at dose reduction	
Imatinib	51 (47.2)
Dasatinib	47 (43.5)
Nilotinib	10 (9.3)
Resistance to at least one TKI before dose reduction	28 (25.9)
CP at diagnosis	108 (100)
Median duration of TKI before dose reduction, months, (range)	69.9 (1-153)
Reason for dose reduction	
Financial burden	23 (21.3)
Attempt for TFR	25 (23.1)
Adverse events	60 (55.6)
In ≥ MR4 at dose reduction, n (%)	
Yes	92 (85.2)
No	16 (14.8)
In ≥ MMR at dose reduction, n (%)	
Yes	98 (90.7)
No	10 (8.7)
Median duration of MR4 before dose reduction, months, (range)	31.6 (0-146)
Median duration to achieve MR4 before dose reduction, months, (range)	15 (2-97)
The median duration of MMR before dose reduction, months, (range)	41.7 (0-146)
Median duration to achieve MMR before dose reduction, months, (range)	10.5 (2-88)
Median follow-up of dose reduction, months, (range)	15 (2-66)

TKI: tyrosine kinase inhibitor; CP: chronic phase, TFR: treatment-free remission; n: number; MMR: major molecular remission; MR4: BCR-ABL IS≤0.01%.

defined as the probability of survival in remaining in MMR and MR4 on low-dose TKI treatment.

Of the 98 patients who achieved MMR at the time of dose reduction, 94 patients (95.9%) experienced maintenance or deeper molecular response, including 94% (47/50) of the patients on imatinib, 97.4% (37/38) of the patients on dasatinib, and 100% of the patients (10/10) on nilotinib. The 1-year and 2-year MRFS in MMR were 96.7% (95% confidence interval [CI]: 90.1-98.9) and 95.1% (95% CI: 87.3-98.2). Moreover, seven of ten patients not in MMR initially, achieved MMR or deeper molecular response with low-dose treatment, with one patient achieving MMR, six achieving MR4 or deeper response. Of 92 patients with MR4, 81 (88.0%) patients maintained MR4 or reached a

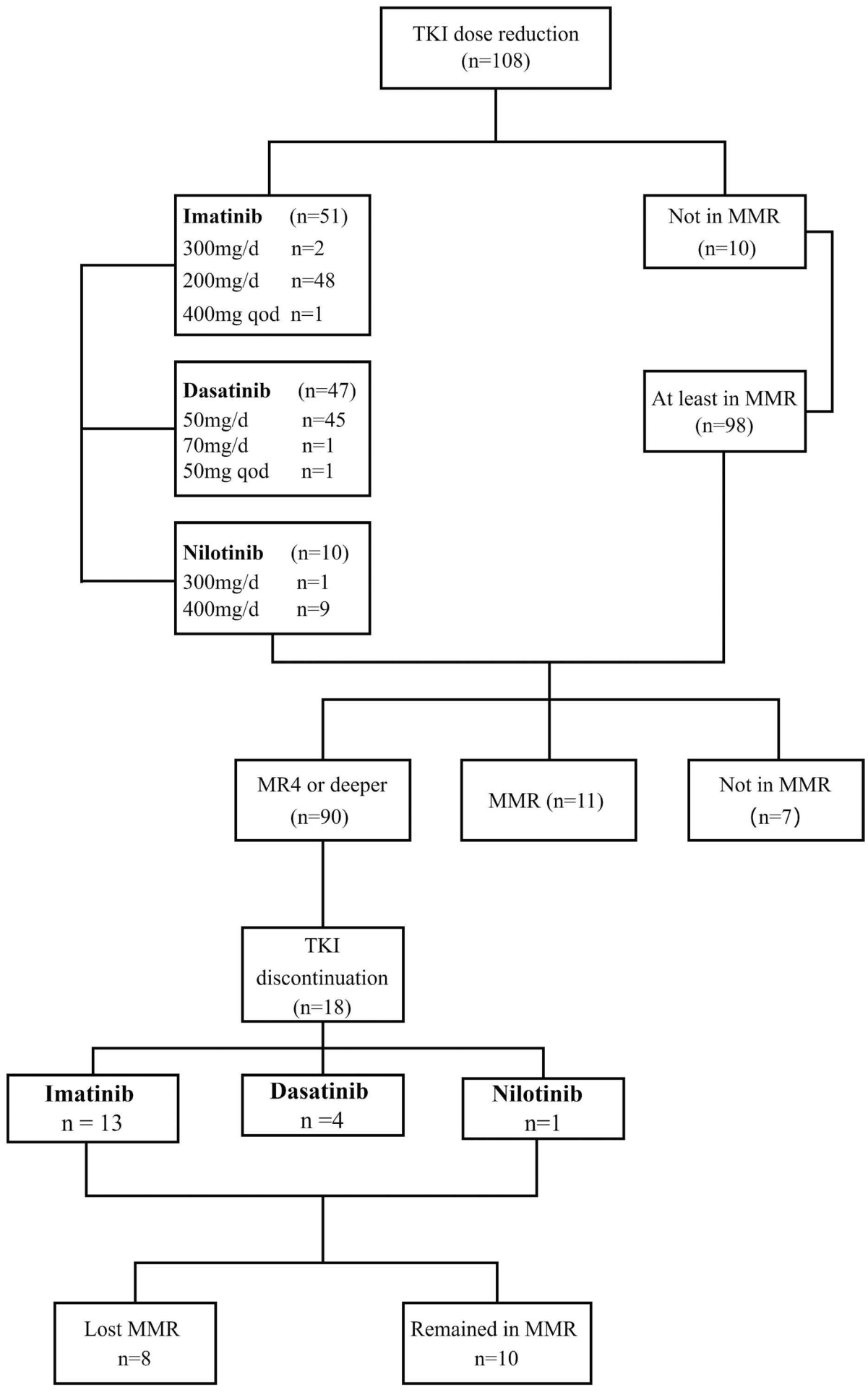

Figure 1. Study population flowchart. TKI:tyrosine kinase inhibitor; MMR: major molecular remission; MR4: BCR-ABL IS≤0.01%. d: day; qod: every other day.

deeper molecular response during dose-reduction. The 1-year and 2-year MRFS in MR4 were 87.8% (95% CI: 78.4-93.3) and 86.1% (95% CI: 76.0-92.1) (Figure 2). Univariate analysis showed that the type of TKI at the time of dose reduction was the only clinical variable significantly associated with MRFS in MR4 (*Online Supplementary Table S1*). The 2-year MRFS in MR4 of patients on imatinib at the time of dose reduction was significantly lower than patients on 2G-TKI, 79.1% (95% CI: 63.2-88.6) *versus* 93.9% (95% CI: 77.2-98.5, log-rank *P*=0.041) (Figure 2).

Four patients who lost MMR returned to a standard dose (n=2) or half standard dose (n=2) of the same TKI, three regained MMR after a median time of 3 months (range, 1.5-10 months), and two regained MR4 after a median time of 7.5 months (range, 3-15 months). A 70-year-old patient who continued to take 50 mg dasatinib due to pleural effusion did not obtain MMR. Seven patients only underwent MR4 loss, all patients regained MR4 after further treatment for 7 months (range, 1-18 months) on the same low-dose TKI.

In this study, a total of 90 patients were in MR4 or deeper response during dose reduction. Sixty six patients were eligible to discontinued TKI therapy according to the eligibility criteria in the EURO-SKI study.[6] Eighteen of the patients (imatinib, n= 13; dasatinib, n=4; nilotinib, n=1) further discontinued low-dose TKI therapy based on their own needs, of which, with six patients fearing adverse effects of long-term treatment, four for financial burden, seven for the pursuit of TFR, and one for pancreatic cancer. The median duration of TKI treatment and MR4 was 87 months (range, 44-128 months) and 58 months (range, 28-125 months), respectively. The median duration of TKI reduction was 21 months (range, 3-66 months). At a median follow-up of 6 months (range, 1-42 months), eight patients lost MMR, of which six patients lost MMR within 6 months. The TFR at 6 months and 12 months was 59.6% (95% CI: 30.7-79.7) and 44.7% (95% CI: 14.3-71.6). Seven patients who restarted the same low-dose TKI achieved MMR after a median follow-up time of 4 months (range, 1-6 month), of which six patients achieved MR4. One patient did not restart TKI due to worsening pancreatic cancer and died of pancreatic cancer.

In the present study, the 1- and 2-year MRFS in MMR for patients on low-dose imatinib were 93.5% (*Online Supplementary Table S1*). In the DESTINY study, where 174 pa-

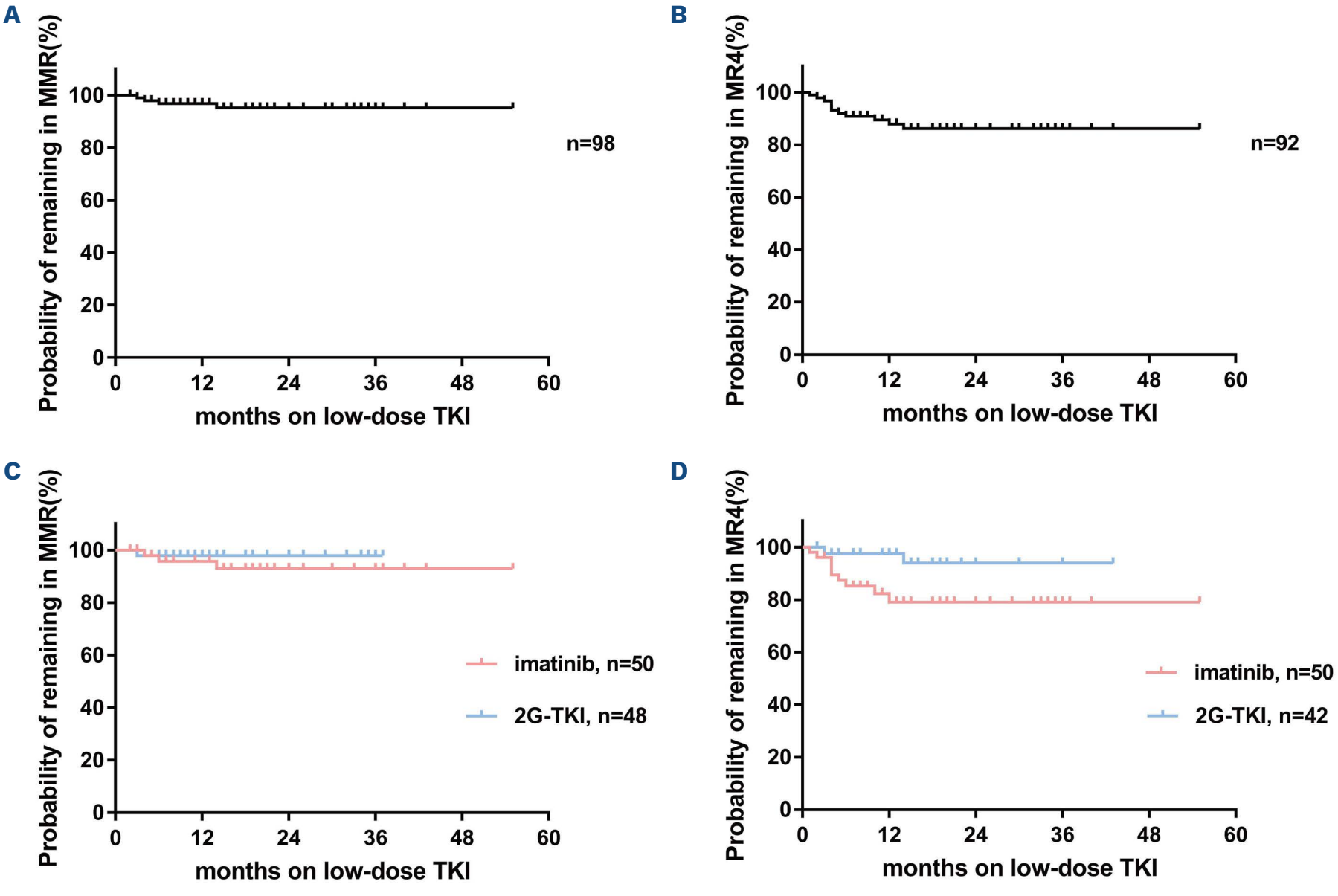

Figure 2. Molecular relapse-free survival after tyrosine kinase inhibitor dose reduction. (A and B) Molecular relapse-free survival (MRFS) in major molecular remission (MMR) and MR4 (BCR-ABL IS≤0.01%) in patients after tyrosine kinase inhibitor (TKI) dose reduction. (C and D) MRFS in MMR and MR4 in patients after TKI dose reduction according to the type of TKI. 2G TKI: second-generation tyrosine kinase inhibitor (nilotinib, dasatinib).

tients (85% patients were on imatinib) at least in MMR received half-dose treatment for 12 months, only 12 patients (7%) experienced molecular recurrence (loss of MMR).[9] 97.4% (37/38) of patients remained in MMR with 50 mg dasatinib or lower, consistent with another study that reported a 3-year MRFS in MMR of 94.5%.[10] Importantly, of nine patients not in MMR, six (66.7%) achieved MMR or deeper molecular response with low dasatinib dose treatment. In our study, all patients (n=10) on half-dose nilotinib experienced maintenance of MMR. Similarly, the NILO-RED study reported a 12-months survival without unconfirmed MMR loss of 97% for 67 patients switching from a standard-dose nilotinib to a half-dose.[11]

Given that MR4 is regarded as the threshold for TKI withdrawal, increased emphasis should be placed on ascertaining whether dose optimization is effective in maintaining MR4. In our study, of 92 patients with MR4, 81 (88.0%) maintained MR4 or attained a deeper molecular response during dose reduction. Similarly, a prospective study reported that most patients (50/52) could maintain MR4 with a lower dose of TKI.[12] In the DESTINY study, patients in MR4 had a higher probability of maintaining MMR than patients only in MMR after 12 months of half-dose therapy (98% *vs*. 71%, *P*=0.0007).[9] Due to the small sample size of patients (n=6) who were only in MMR in this study, the difference in MMR maintenance between the MR4 and MMR groups was not analyzed. Interestingly, we found patients with second-generation tyrosine kinase inhibitor (2G TKI) at dose reduction had a higher probability of remaining in MR4. Consistently, in a multiple TKI discontinuation study, patients with 2-3G TKI experienced increased TFR compared to patients with imatinib.[13] In our study, at the last follow-up, we observed an improved molecular response in three of the six (50.0%) patients who were only in MMR at dose reduction.

It is well-established that in clinical practice, dose optimization is important to maintain efficacy and mitigate adverse effects related to TKI. A French study previously reported that 23% (196/853) of patients treated with dasatinib experienced different degrees of pleural effusion, of which 59.2% (116/196) patients required a reduced dose.[14] In the present study, 71.8% (28/39) of patients received lower dasatinib doses due to pleural effusion (*Online Supplementary Table S2*). The pleural effusion in all cases alleviated or disappeared after low-dose treatment (50 mg/d, n=27; 50 mg qod, n=1), of which 12 received diuretic therapy. Eighteen patients underwent imatinib dose reductions (200 mg/d, n=16; 300 mg/d, n=2) mainly for leukopenia, anemia, fatigue edema, and rash itching. Nilotinib was reduced to 300 mg (n=1) and 400 mg (n=2) due to bone pain and elevated bilirubin (*Online Supplementary Table S2*). Similarly, all adverse events caused by imatinib and nilotinib were relieved or resolved with low-dose treatment.

The DESTINY study reported a recurrence-free survival at 24 months after stopping TKI of 72%,[8] higher than the reported TFR (50%) at 24 months in the EURO-SKI study.[6] Similarly, Claudiani *et al.* reported the 2-year TFRS of patients with low-dose treatment was 74.1%,[10] and they considered that low-dose TKI might improve the chances of obtaining TFR by extending the duration of TKI and MR4. Eighteen of our patients with at least MR4 discontinued TKI after 21 months (range, 3-66 months) of low-dose treatment. A total of eight patients lost MMR, of which six patients lost MMR within 6 months. The TFR at 6 and 12 months was 59.6% and 44.7%, in agreement with the EURO-SKI study.[6] Another study found that full-dose group and low-dose group displayed a similar TFR at 60 months after TKI cessation (47.5% *vs*. 58.8%, *P*=0.14), indicting low-dose TKI before discontinuation do not impair TFR.[15] Nonetheless, it remains unclear whether TKI dose reduction prior to discontinuation can improve TFR. Consistent with the literature, our findings showed that low-dose TKI did not affect the achievement of TFR.

In conclusion, the present study provides evidence that low-dose therapy can address the needs of the majority of patients, including alleviation of financial burden, preparation before discontinuation, and reduction of adverse effects. However, our study still has some shortcomings. Firstly, this is a retrospective study with a small group of patients that only obtained MMR. Thus, we did not compare the difference in molecular response after dose reduction between patients who obtained MMR only and those who obtained MR4. In addition, only 18 patients discontinued low-dose TKI in this study, and the data on discontinuation after dose reduction might be biased. Importantly, prospective clinical studies with large patient numbers are warranted to corroborate the effect of dose reduction.

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Contributions

YLC, ZLL, JZ, FJC, YLZ and WML designed research, collected data, and wrote the manuscript; YLC, ZLL and JZ interpreted the data and performed statistical analysis; YLC and WML designed and supervised the overall study; DYW, WJH and LM collected data and reviewed the manuscript.

Data-sharing statement

The data used to support the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available due to privacy or ethical restrictions.

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