De-escalation or discontinuation of tyrosine kinase inhibitor in patients with chronic myeloid leukemia: A multicentral, open-label, prospective trial in China

Jie Luo1 | Xin Du2 | Jin Lou2 | Jianwei Wu3 | Liping Ma4 | Jixian Huang5 | Liangtuo Wang6 | Chuanqing Tu7 | Zelin Liu8 | Liya Chen9 | Yaxian Tan1 | Dongmei Luo1 | Hanyin Liang1 | Changxin Yin1 | Rui Cao1 | Xuan Zhou1 | Qifa Liu1 | Xiaoli Liu1 | Na Xu1

1Department of Hematology, Nanfang Hospital, Southern Medical University, Guangzhou, China
2Department of Hematology, Shenzhen Second People’s Hospital, The First Affiliated Hospital of Shenzhen University, Shenzhen University School of Medicine, Shenzhen, China
3Department of Hematology, Jinan University Affiliated Jiangmen Hospital of Traditional Chinese Medicine, Jiangmen, Guangdong, China
4Department of Hematology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China
5Department of Hematology, Yuebei People’s Hospital, Shantou University, Shaoguan, Guangdong, China
6Department of Hematology, People’s hospital of Yang Jiang, Yang Jiang, Guangdong, China
7Department of Hematology, Bao’ an District People Hospital, The Second Affiliated Hospital of Shenzhen University, Shenzhen, China
8Department of Hematology, Huazhong University of Science and Technology Union Shenzhen Hospital (Nanshan Hospital), Shenzhen, China
9Department of Medical Quality Management, Nanfang Hospital, Southern Medical University, Guangzhou, China

Correspondence
Qifa Liu, Department of Hematology, Nanfang Hospital, Southern Medical University, Guangzhou 510515, China.
Email: liuqifa628@163.com

Xiaoli Liu, Department of Hematology, Nanfang Hospital, Southern Medical University, Guangzhou 510515, China.
Email: lx2405@126.com

Na Xu, Department of Hematology, Nanfang Hospital, Southern Medical University, Guangzhou 510515, China.
Email: sprenaa@163.com

Abstract

Background: Long-term treatment-free remission (TFR) represents a new goal for chronic myeloid leukemia (CML). Optimizing dose of tyrosine kinase inhibitors (TKIs) in the CML treatment maybe a new challenge to maintain effective and improving patients’ quality of life. We hypothesized that administration of low-dose TKIs does not compromise major molecular response (MMR) in patients with CML who have a deep molecular response (DMR).

Methods: We did an open-label, randomized trial at eight hospitals in China. Eligible CML-CP patients (aged 18–70 years) had shown continuous response to TKI more than 5 years and maintained MR4.5 (BCR-ABL IS ≤ 0.0032%) in recent 18 months. Patients were randomly assigned (1:1) to the TKI de-escalation group or the discontinuation group. Recurrence was defined as the single sample with real time Quantitative PCR (RT-qPCR) measurement.
greater than 0.1% (MMR). The primary endpoint was 12-month MMR rate in patients who received de-escalation or discontinuation of TKIs. This study was registered at ClinicalTrials.gov (NCT04143087).

Results: Around 125 patients were enrolled between October 23, 2019 and October 31, 2020, 62 patients received dose-de-escalation of TKIs, while 63 patients in the discontinuation group. In the de-escalation group, molecular recurrence-free survival at 12 months was 88.32% (95% CI 79%–98%), whereas molecular recurrence-free survival in the discontinuation group at 12 months was 59.98% (95% CI 47–73). No progressions occurred at the data cut-off date. All 29 recurrence cases restart TKI treatment returned to MMR. Cytolytic NK cells as a proportion of lymphocyte cells were significantly increased from baseline after 6 months whether in the de-escalation or TKIs cessation group (P = 0.048, 0.001, respectively); compared with the relapsing patients, Tregs proportion was decreased (P = 0.003), and higher proportion of NK cells were found in non-relapsing patients whether in TKI de-escalation or discontinuation group (P = 0.011, 0.007, respectively). We also found that the de-escalation group showed better disease-specific HRQOL in regards to its impact on emotional functioning, fatigue, pain, and financial difficulties.

Conclusion: With 88.32% MMR in 12-months follow-up after de-escalation TKIs’ treatment, dose-halving could become a new treatment paradigm for CML patients who with DMR under continuing maintenance therapy with TKIs.

KEYWORDS
chronic myeloid leukemia, de-escalation TKI, treatment-free remission

1 | INTRODUCTION

Tyrosine kinase inhibitors (TKIs) had dramatically improved the treatment and prognosis of chronic myeloid leukemia (CML) patients. The life expectancy of most CML patients is similar to healthy age matched individuals [1, 2]. A new goal for treating CML is survival at good quality of life, with treatment discontinuation in sustained deep molecular response (DMR) and treatment-free remission (TFR). Unexpectedly, the benefit of TFR policy is restricted to no more than 15%–25% of all CML patient population [3–5]. Meaning the majority of patients are at risk of lifelong exposure to TKIs, long-term treatment with TKIs is accompanied with high cost of TKIs and adverse events (AEs), which negatively impact patients’ quality of life and may even cause significant morbidity and mortality [6].

TKIs’ dose de-escalation is considered as a way of dealing with such problems. Recently, retrospective analyses of large-cohort clinical trials have shown that TKIs dose reduction did not compromise efficacy and improved patients’ quality of life [5, 7]. Furthermore, the DESTINY trial showed that de-escalation of TKIs may improve TFR than discontinuation [8–10]. Fassoni et al. [11] used a mathematical model to verify that dose-halving TKI does not lead to a reduction of long-term treatment efficiency patients who have already achieved sustained remission. While there was substantial data on efficacy and safety of TKI dose reduction, but there was lack of the underlying mechanism and health-related quality of life (HRQOL) data of patients with TKIs’ dose reduction.

Immunologic surveillance of residual leukemic cells (LC) is hypothesized to be one of the critical factors in successful TFR [5, 12]. DMR is associated with increased NK and CD8+ T-cell numbers, and decreased Tregs in the peripheral blood of CML patients. Likewise, successful TFR has been linked to increased NK/CD8+ T-cells and decreased Tregs [5, 13–14]. However, it is an ambiguous inference of individual immunologic configurations based on TKI dose reduction.

All TKIs have potential immunosuppressive effects. Therefore, we performed this multicenter study to explore impact of dose de-escalation or discontinuation on Chinese CML patients, aiming to provide some evidence about optimizing dose of TKIs.

2 | METHODS

2.1 | Study design and participants

This trial was conducted at eight hospitals in China. The inclusion criteria include: age ≥18 years; in first chronic phase with a known BCR-ABL1 transcript (any transcript type was permitted); ≥5 years of therapy with full dose of TKIs’ therapy (either imatinib, nilotinib, or dasatinib); had monitored the BCR-ABL1 transcripts frequently
through real time Quantitative PCR (RT-qPCR) analysis in recent 18 months, each with 32,000 or more ABL1 control transcripts and had persistent BCR-ABL1 ≤0.0032% (also known as MR4.5, defined as a 4.5-log reduction in the BCR-ABL1 transcript according to the international scale). Patients at the accelerated phase (AP)/blast crisis (BC) of CML, or combined with mutations in the ABL kinase region, patients who received allogeneic hematopoietic stem-cell transplantation, or were treated with any other immunotherapy except interferon, and pregnancy or breastfeeding, were excluded from this study.

All individual entrants provided written informed consent before enrollment, and the trial was conducted in line with the principles of the Declaration of Helsinki. This study was registered at ClinicalTrials.gov (NCT04143087).

2.2 | TKIs dose procedure

Eligible patients were randomly allocated to TKIs’ de-escalation group or discontinuation group. In the de-escalation group, participants dose-halving TKIs: imatinib 200 mg once daily, dasatinib 50 mg once daily, or nilotinib 300 mg or 400 mg once daily. RT-qPCR analyses were done monthly for the first 6 months, every 2 months for the subsequent 6 months, and we expressed all BCR-ABL1 ratios according to the international scale. Molecular recurrence was defined as loss of major molecular response (MMR; BCR-ABL1 IS > 0.1%) at a single time-point. In these cases, all patients were required to readministered TKIs with entry dose, and we continued monitoring monthly until MMR was reached again.

Lymphocyte subsets were examined by flow cytometry at trial entry, after 6 months of half-dose therapy and treatment cessation, and when patients molecular relapse. The lymphocyte fraction was examined by flow cytometry with FACSCalibur cytometer and BD Cell Quest software, version 3.3 (Becton Dickinson, Franklin Lakes, NJ, USA). All antibodies were purchased from Becton Dickinson. The lymphocyte subsets were defined as follows: CD3+ T cells, CD4 T cells (CD3+CD4+), CD8 T cells (CD3+CD8+), NK cells (CD3−CD56+, CD3−CD56−CD16+ and CD3−CD56−CD16−), T regulatory cells (CD3+CD4+CD25highCD127−Foxp3+), B cells (CD19+).

HRQOL was accessed with the EORTC QLQ-C30 questionnaire in 6 months after patients’ enrollment [15], which was composed of 15 territories and 30-item measures, including five functional scales: physical, role, cognitive, emotional, and social functioning; three symptom scales: fatigue, pain, nausea, and vomiting; six single items and a global QOL scale. Except the global QOL scale was rated using a positive score range 1–7, the other parameters were rated using a four-point score (1 = not at all, 2 = a little bit, 3 = quite a bit, 4 = very much). In order to make the scores in each domain comparable, we converted the raw scores into standard scores with a value of 0–100. Notably, higher scores on functional and global QOL scales indicate better functioning, whereas higher scores on symptom scales indicate greater symptom burden.

2.3 | Outcomes

The primary end-point of this study was the MMR rate after a follow-up of 12 months in patients who received de-escalation or discontinuation of TKIs. The secondary endpoints include: proportion of relapsed patients who regained molecular remission after TKIs’ re-challenge, and time to MMR recovery (defined as the time from the date of confirmed loss of MMR to the date of MMR recovery) and survival; and the immunologic configurations based on treatment alterations; the difference of HRQOL between the de-escalation and the discontinuation group.

2.4 | Statistical analysis

The sample size was required to provide the study with a significance level of 0.05 and a power of 90%; calculated assuming a worst-case scenario (TKI stop proportion of relapsing patients = 0.5; TKI de-escalation proportion of relapsing patients = 0.8; group allocation of 1:1 in either direction; 11% dropouts), and estimated that a minimum of total planned sample size was 117 patients (58 in one group, 59 in another group).

We structured the trial as two cohorts, de-escalation group and discontinuation group. Statistical analyses were done with IBM-SPSS software package, version 22. No adjustment for multiple testing or missing data was incorporated. Continuous variables were summarized using median and ranges, categorical variables were expressed as frequencies and proportions. Descriptive analyses comparing cohorts were performed using the chi-square test, Wilcoxon matched-pairs signed ranked test, or Mann–Whitney U-test. The molecular relapse-free survival was estimated using the Kaplan–Meier method and reported with 95% confidence interval (CI), comparison of survival curves was performed using the log-rank test through GraphPad Prism v7(GraphPad Software Inc, La Jolla, CA, USA). For the estimation of time to MMR recovery, cumulative incidence analysis was used. Univariate and multivariate Cox regression analyses were used to select the factors impact on successful recurrence-free survival from various trial entry characteristics. p < 0.05 was considered significant.

3 | RESULTS

3.1 | Patient characteristics

The trial was conducted between October 23, 2019 and October 31, 2020 at eight centers in South China, 188 patients were screened and 63 (33.51%) were excluded (Figure 1). These were composed of 41 patients who withdrew due to concern over additional visits and RT-qPCR analyses (requested monthly for the first 6 months, every 2 months for the subsequent 6 months), and 22 who were ineligible (18 combined with mutations in the ABL kinase region, 4 pregnancy).
Baseline demographic and clinical characteristics of the 125 patients enrolled in this trial

|                       | TKI de-escalation (n = 62) | TKI discontinuation (n = 63) | Overall (n = 125) | P  |
|-----------------------|----------------------------|-------------------------------|------------------|----|
| Median age (years)    | 49 (18–76)                 | 47 (18–82)                   | 48 (18–82)       | 0.061 |
| Sex                   |                            |                               |                  | 0.328 |
| Male                  | 29 (47%)                   | 35 (56%)                     | 64 (51%)         |    |
| Female                | 33 (53%)                   | 28 (44%)                     | 61 (49%)         |    |
| Sokal risk            |                            |                               |                  | 0.816 |
| Low                   | 33 (53%)                   | 35 (56%)                     | 68 (54%)         |    |
| Intermediate          | 22 (35%)                   | 21 (33%)                     | 43 (34%)         |    |
| High                  | 7 (11%)                    | 7 (11%)                      | 14 (11%)         |    |
| Previous IFN therapy  |                            |                               |                  | 0.979 |
| Yes                   | 5 (8%)                     | 5 (8%)                        | 10 (8%)          |    |
| No                    | 57 (92%)                   | 58 (92%)                     | 115 (92%)        |    |
| Medication            |                            |                               |                  | 0.585 |
| Imatinib              | 48 (77%)                   | 52 (82%)                     | 100 (80%)        |    |
| Nilotinib             | 6 (10%)                    | 8 (13%)                      | 14 (11%)         |    |
| Dasatinib             | 8 (13%)                    | 3 (5%)                       | 11 (8%)          |    |
| First-line treatment  |                            |                               |                  | 0.452 |
| Resistance            | 3 (5%)                     | 2 (3%)                       | 5 (4%)           |    |
| Intolerance           | 2 (3%)                     | 1 (2%)                       | 3 (2%)           |    |
| Median duration of TKIs (months) | 72 (60–168) | 79 (60–180)       | 72 (60–180)     | 0.152 |
| Median duration in MR4.5 (months) | 36 (18–156) | 40 (18–124)       | 36 (18–156)     | 0.052 |

Note: There was no significant difference in baseline demographic and clinical characteristics between TKI de-escalation and discontinuation groups. TKIs, tyrosine kinase inhibitors; MR4.5, deep molecular response (BCR-ABL ≤ 0.0032%).

FIGURE 1  Trial profile

A total of 125 patients enrolled in this study, 62 patients enrolled into the de-escalation group and 63 patients enter into the discontinuation group (Figure 1). Baseline demographic and clinical characteristics were summarized in Table 1. The median duration of TKI therapy was 72 months (range 60–168 months) in the de-escalation cohort and 79 months (range 60–180 months) in the discontinuation cohort, whereas the median duration of MR4.5 was 36 months (range 18–156 months) and 40 months (range 18–124 months), respectively. Although these differences in baseline characteristics were not significant.

3.2  Molecular relapses and molecular relapse-free survival

During the 12 months of half-dose therapy, 5 patients (8.06%) had molecular recurrence (loss of MMR), whereas molecular recurrence was seen in 24 patients (38.10%) in the discontinuation group. Molecular recurrence-free survival was significantly lower in the discontinued group [59.98% (95% CI 47–73) versus 88.32% (95% CI 79–98); p = 0.0002; Figure 2A].

Patients with recurrences were required to resume the full dose of their entry TKI, and all complied with this. Of the 29 recurrences across the trial, 27 returned to MMR within 5 months of TKI resumption, with no significant difference (p = 0.90) between the discontinuation group and the de-escalation group. Another two patients in the discontinuation group opted to dasatinib (their entry TKI) 50 mg once daily less than full dose, and returned to MMR within 6 months. Notably,
During 12-month follow-up, no death cases reported and no patient underwent disease progression to AP/BC of CML.

During the 12-month observation period, TKI-related AEs (nausea and vomiting, diarrhea, anorexia, abdominal discomfort, and night sweat) all improved in both groups. However, we have found that there were 24%, 28.8%, and 15.2% patients complained about aggravation or new development of fatigue, musculoskeletal pain, and pruritus after TKI de-escalation or discontinuation (Table 2). And these three worsened or newly developed symptoms were more occurred in the discontinuation group, the incidence of musculoskeletal pain shows the significant difference between the two groups (P = 0.021). Musculoskeletal pain was involved to the whole body particularly the upper joint, and it can be controlled by non-steroidal anti-inflammatory drugs (NSAID) with the median duration time of 5 months.

### 3.3 Predictive factors for molecular recurrence

The risk of recurrence of patients in the discontinuation group was 4.94 times than in the de-escalation group (95% CI 1.89–12.89, P = 0.001; Table 3). In univariate analysis, no correlation was seen in the Sokal score and medication with recurrence in the discontinuation or the de-escalation group. But a significant association was found among patients with continuous TKI treatment and the longer duration of MR4.5, and the fewer of recurrences. Patients who treated ongoing TKIs for more than 6 years had a 0.36 times greater risk of recurrence than those treated less than 6 years (95% CI 0.18–0.75, P = 0.006; Table 3), and maintained MR4.5 for less than 36 months were 3.33 times more likely to relapse than those maintained over 3 years (95% CI 0.14–0.62, P = 0.001; Table 3).
| Table 2 | Aggravation or new development symptoms after TKI de-escalation or discontinuation (N, %) |
|---------|------------------------------------------------------------------------------------------|
| Symptoms | De-escalation | Discontinuation | Total | P value |
| Fatigue | 14 (22.58%) | 16 (25.4%) | 30 (24%) | 0.712 |
| Grade 1–2 | 13 | 10 | 23 |
| Grade 3–4 | 1 | 6 | 7 |
| Musculoskeletal pain | 12 (19.23%) | 24 (33.33%) | 36 (28.8%) | 0.021 |
| Grade 1–2 | 11 | 21 | 32 |
| Grade 3–4 | 1 | 3 | 4 |
| Pruritus | 7 (11.54%) | 12 (19.05%) | 19 (15.2%) | 0.227 |
| Grade 1–2 | 6 | 9 | 15 |
| Grade 3–4 | 1 | 3 | 4 |

| Table 3 | Univariate and multivariable analysis of various parameters’ associations with molecular recurrence |
|---------|------------------------------------------------------------------------------------------------|
| Characteristic | Univariate | Multivariable |
| | HR (95% CI) | P value | HR (95% CI) | P value |
| Group | De-escalation vs. discontinuation | 4.94 (1.89–12.89) | 0.001* | 6.47 (2.62–16.00) | <0.001* |
| Sokal score | Low vs. high to intermediate | 1.61 (0.79–3.29) | 0.192 |
| Medication | Imatinib vs. second generation | 1.47 (0.63–3.41) | 0.375 |
| Median duration of TKIs (months) | <72 vs. ≥72 | 0.36 (0.18–0.75) | 0.006* | 0.41 (0.19–0.89) | 0.024* |
| Median duration in MR (months) |  <36 vs. ≥36 | 0.30 (0.14–0.62) | 0.001* | 0.26 (0.14–0.57) | 0.001* |

Note: Where relevant, the HR refers to the probability of recurrence for the parameter relative to the comparable one (e.g., de-escalation vs. discontinuation, male vs. female, Sokal score low risk vs. high to intermediate risk). HR, hazard ratio. Second generation = nilotinib and dasatinib. TKIs, tyrosine kinase inhibitors; MR4.5, deep molecular response (BCR-ABL ≤ 0.0032%). *P < 0.05 was considered statistically significant.

Using the backward elimination method, a p-value of 0.1 acts as a threshold to enroll in the multivariate analysis. The variables included in the multivariate analysis in this trial are as follows: group, total TKI treatment time, and duration of MR4.5. The results showed that de-escalation group, longer duration of TKI treatment, and the time of MR4.5 maintained were the protective factor in molecular remission (Table 3).

### 3.4 The effect on immune function of de-escalating/discontinuing TKIs

Here, we collected immunological subsets in trial entry and after 6 months of the half-dose therapy or cessation TKIs. Cytolytic NK cells (CD3–CD56+CD16+) as a proportion of NK cells were significantly increased at 6 months in the de-escalation group compared with baseline (P = 0.048; Table 4). Although the proportion of the other lymphocyte subsets was slightly changed after 6 months of de-escalation, but the changes were not statistically significant (Table 4). Simultaneously, the percentage of immunological subsets we assessed was somewhat higher at 6 months in the discontinuation group compared with the trial initial, among them, NK cells’ (CD3–CD56+) proportion was significantly increased after 6 months of TKIs’ cessation (P = 0.001; Table 5). To explore the relationship between autoimmune recovery and molecular recurrence, we analyzed the lymphocyte subsets in all patients (29 cases had recurrence and 96 cases had successful relapse-free survival). We observed that comparing with the relapsed patients, Tregs as a percentage of lymphocytes were decreased (P = 0.003, Table 6, Figure 3), and higher proportion of NK cells were occurred in the non-relapsing group at TKI de-escalation or discontinuation (P = 0.011, 0.007, respectively, Table 6, Figure 3). And no significant association was seen between any other subset and molecular relapse.

### 3.5 Health-related quality of life

Table 7 gives the quality of life for each group that is assessed 6 months after enrollment. No significant difference was seen between
TABLE 4  Changes of de-escalation group in lymphocyte subsets compared with baseline (n = 62, median, range)

| Subsets | Baseline | De-escalation | Z value | P value |
|---------|----------|---------------|---------|---------|
| CD3⁺    | 67.83 (50.70–75.95) | 67.15 (56.61–78.96) | −0.145 | 0.145   |
| CD3⁺CD4⁺| 35.83 (28.40–44.67) | 36.37 (23.95–41.33) | −1.739 | 0.082   |
| CD3⁺CD8⁺| 26.59 (16.20–38.10) | 26.48 (15.32–35.06) | −0.729 | 0.466   |
| CD19⁺   | 10.07 (3.15–16.80)  | 9.47 (4.75–16.75)  | −1.658 | 0.097   |
| CD3⁺CD4⁺CD25⁺CD127⁻Foxp3⁺| 1.96 (0.35–4.40) | 1.94 (0.37–4.00) | −0.799 | 0.424   |
| CD3⁻CD56⁺ | 15.59 (8.50–21.20) | 17.78 (7.01–35.30) | −2.550 | 0.011*  |

*The Wilcoxon matched-pairs signed ranked test was used to compare variables between de-escalation group and baseline with a level of significance of 0.05.

TABLE 5  Changes of discontinuation group in lymphocyte subsets compared with baseline (n = 63, median, range)

| Subsets | Baseline | Discontinuation | Z value | P value |
|---------|----------|----------------|---------|---------|
| CD3⁺    | 65.00 (50.24–74.00) | 65.24 (48.93–74.87) | −1.599 | 0.110   |
| CD3⁺CD4⁺| 31.32 (17.06–47.93) | 32.56 (19.27–45.97) | −0.084 | 0.933   |
| CD3⁺CD8⁺| 27.76 (19.98–42.18) | 28.22 (16.21–37.40) | −1.451 | 0.147   |
| CD19⁺   | 10.34 (5.45–20.24)  | 10.50 (5.48–18.92) | −1.458 | 0.145   |
| CD3⁺CD4⁺CD25⁺CD127⁻Foxp3⁺| 1.75 (0.78–4.26) | 1.75 (0.51–4.32) | −1.085 | 0.278   |
| CD3⁻CD56⁺ | 15.31 (7.31–24.68) | 15.43 (8.04–41.26) | −3.430 | 0.001*  |
| CD3⁻CD56⁺CD16⁺ | 0.84 (0.00–10.02) | 1.19 (0.00–14.01) | −0.287 | 0.774   |

*The Wilcoxon matched-pairs signed ranked test was used to compare variables between discontinuation group and baseline with a level of significance of 0.05.

TABLE 6  Changes in lymphocyte subsets at TKIs de-escalation or discontinuation group in MMR and relapsing patients (n = 125, median, range)

| Subsets | Relapsing (n = 29) median (range) | MMR (n = 96) median (range) | Z value | P value |
|---------|----------------------------------|-------------------------------|---------|---------|
| CD3⁺    | 67.99 (60.13–75.95)              | 65.57 (50.24–74.82)           | −0.297  | 0.766   |
| CD3⁺CD4⁺| 34.15 (17.06–42.01)              | 32.64 (25.10–47.93)           | −0.832  | 0.406   |
| CD3⁺CD8⁺| 28.51 (19.98–42.18)              | 26.25 (16.20–38.10)           | −1.921  | 0.055   |
| CD19⁺   | 9.94 (5.45–15.46)                | 10.34 (3.15–20.24)            | −0.823  | 0.410   |
| CD3⁺CD4⁺CD25⁺CD127⁻Foxp3⁺| 2.24 (0.78–4.26) | 1.67 (0.35–4.40) | −2.985 | 0.003*  |
| CD3⁺CD56⁺| 15.59 (8.50–21.20)              | 17.78 (7.01–35.30)            | −2.550  | 0.011*  |
| CD3⁺CD56⁺CD16⁺ | 0.12 (0.00–6.41) | 1.33 (0.00–98.08) | −2.688 | 0.007*  |

*The Mann–Whitney U-test was used to compare variables from relapsing and non-relapsing patients with a level of significance of 0.05.

the two groups regarding the overall health status scores (P = 0.889). The functional section of the groups was roughly the same, but the emotional functioning tended to be worse in the discontinuation group (the median scores were 75 vs. 83.33, P = 0.038). In terms of symptom scales, fatigue, pain, and pruritus in the de-escalation group were less frequent (the median scores were 22.22 vs. 33.33, 0 vs. 16.67, 0 vs. 33.33; P = 0.024, 0.03, 0.505, respectively). Although the median score of financial difficulties was the same, more patients in the discontinuation set were faced with more severe financial burden [scores ≥ 66.67 in the two groups were 10 patients (15.87%) vs. 5 patients (8.06%), P = 0.036]. There were no significant differences between the two groups in the other symptom burden.

Next, we analyzed the four items in emotional functioning: tension, trepidation, irritability, and depression, to identify which items bothered the patients most. Figure 4 displays that CML patients showed more tension and trepidation of disease, and people in the discontinuation cohort had higher prevalence and more moderate or severe tension and trepidation of disease than the de-escalation one [19 patients (30.16%) vs. 6 patients (9.68%); 18 patients (28.57%) vs. 9 patients (14.52%), respectively]. When asked the reasons why they feel so nervous and worried about their sickness, the majority of patients...
complained that molecular recurrence after discontinuing was their biggest concern.

4 | DISCUSSION

There has been considerable interest in TFR of CML in the past few years, with most studies typically showing recurrence-free survival (defined as loss of MMR) of 50%–60% in the first chronic phase patients on the TKI therapy for some years and in stable MR4 [4]. The current TKI discontinuation strategies are still too far because of residual LC and leukemia stem cells (LSCs) that cannot be eliminated by patient-specific immunological mechanisms [5, 16]. Dose optimization of TKIs maybe minimizing side-effects associated with continuous TKI therapy is required [7]. In our study, 125 patients were enrolled into the de-escalation group or the discontinuation group, and there were no differences of basic characteristics between two groups. Follow-up for 12 months, the relapse-free survival in the de-escalation set was significantly superior to the discontinuation set [88.32% (95% CI 79–98) vs. 59.98% (95% CI 47–73), P = 0.0002]. The proportion of patients who had molecular recurrence (loss of MMR) in the half-dose group was similar to the de-escalation phase in DESTINY trial (8.06% vs. 7%) [8], and estimated TFR rate in the discontinuation group was aligned with other prospective studies that had reported data (59.98% vs. 50%–60%) [4]. After 12 months, the frequency of BCR-ABL1 assessed was maintained at every 3 months. Follow-up up to now (26 months), as shown in Figure 2A, there were two patients with late relapse in the discontinuation group, who relapsed at months 22 and 25, respectively, and the relapse-free survival rate decreased to 54.51%. While no new relapse was observed in the de-escalation group. In our study, 29 patients occurred molecular relapses, all patients returned to MMR within 6 months of TKI resumption. Monitoring BCR-ABL1 IS transcript level frequently is beneficial to detect the loss of MMR timely and re-administer TKIs early. There were no death or disease progression cases during the 12-month follow-up, indicating that reduction or stop of TKIs is feasible and safe for CML-CP patients who in DMR.

Duration of the treatment before cessation TKIs was reported as a prognostic factor in many studies [9, 17]. In the EUROSKI study [17], the benefit of the additional treatment on recurrence-free survival is 3% per additional year, this proportion is 4% in the DESTINY trial [8]. In our analysis, the recurrence rate of patients who accepted TKIs for over 6 years was lower than those treated less than 72 months (12/71, 16.90% vs. 19/54, 35.19%). These results displayed that longer the duration of the TKI treatment, the lower the recurrence rate.
TABLE 7  EORTC QOL-C30 scales and other items

|                      | TKI de-escalation (n = 62) | TKI discontinuation (n = 63) | P value* |
|----------------------|-----------------------------|-------------------------------|----------|
| **Global health status** |                             |                               |          |
|                      |                             |                               | 0.889    |
| **Functional scales** |                             |                               |          |
| Physical functioning | 93.33 (40–100)              | 86.67 (40–93.33)              | 0.863    |
| Role functioning     | 83.33 (0–83.33)             | 83.33 (16.67–83.33)           | 0.957    |
| Cognitive functioning| 83.33 (16.67–100)           | 83.33 (16.67–100)             | 0.938    |
| Emotional functioning| 83.33 (50–100)              | 75.00 (25–100)                | 0.038*   |
| Social functioning   | 66.67 (0–83.33)             | 66.67 (33.33–83.33)           | 0.097    |
| **Symptom scales/items** |                           |                               |          |
| Fatigue              | 22.22 (0–66.67)             | 33.33 (0–100)                 | 0.024*   |
| Pain                 | 0.00 (0–50)                 | 16.67 (0–100)                 | 0.030*   |
| Nausea and vomiting  | 16.67 (0–66.67)             | 16.67 (0–100)                 | 0.750    |
| Dyspnea              | 0.00 (0–33.33)              | 0.00 (0–33.33)                | 0.859    |
| Insomnia             | 33.33 (0–66.67)             | 33.33 (0–100)                 | 0.936    |
| Appetite loss        | 33.33 (33.33–100)           | 33.33 (0–100)                 | 0.441    |
| Constipation         | 0.00 (0–66.67)              | 0.00 (0–33.33)                | 0.673    |
| Diarrhea             | 0.00 (0–66.67)              | 0.00 (0–66.67)                | 0.459    |
| Financial difficulties| 33.33 (0–66.67)             | 33.33 (0–100)                 | 0.036*   |
| Pruritus             | 0.00 (0–100)                | 33.33 (0–100)                 | 0.505    |
| Edema                | 0.00 (0–100)                | 0.00 (0–100)                  | 0.809    |

Note: EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30. The Mann-Whitney U-test was used to compare variables from TKI de-escalation and discontinuation group with a level of significance of 0.05.

after de-escalation or discontinuation. We also observed that longer maintaining DMR was predictive for a better outcome, this is consistent with the stop imatinib study (STIM) and the Italy study [18, 19]. Besides, compared with imatinib, the second generation TKIs as first-line treatment could induce DMR faster, and the second generation TKIs’ first-line discontinuation trial showed that the relative recurrence risk was reduced to at least 9% [19, 20]. Unfortunately, due to the low usage of the second generation TKIs in our study, this advantage was not presented.

All TKIs have potential immunosuppressive effects [21]. In our study, TKIs cessation was accompanied by a significant increase in CD3–CD56+ NK cells, this is consistent with the inhibitory effect of TKIs on NK-cell expansion in vitro. And the other lymphocyte subsets also experienced increasing after TKIs discontinuing, as observed by Rea et al. [22]. Alternatively, TKI de-escalation may modify anti-leukemic immune responses, in this study, we found that cytolytic NK cells were significantly increased from baseline after 6 months whether in the de-escalation or TKIs' cessation group. The immune reconstitution that occurs as a consequence of the TFR, maximal restoration of immune responses occurred only in MR4.5, increased NK-cell and effector-T cell cytolytic function, reduced T-cell PD-1 expression and reduced numbers of monocytic myeloid-derived suppressor cells (MDSCs) [21]. Some trials also detected that treatment in discontinuation is more successful in patients with lower expression of CD4+PD-1+ cells and less successful with higher proportion of MDSCs and CD86+ plasmacytoid dendritic cells [10, 13]. Herein, we presented that compared with relapsing patients, the proportion of immunosuppressive cells’ Tregs was decreased and the proportion of CD3+CD56+ NK cells which can exert detrimental effects to cancer cells was increased in those achieving good clinical results after de-escalating or discontinuing, these results were consistent with the EUROSKI [17].

Recently, Harrington et al. [23] found that patients with 50 mg dose of dasatinib had significantly higher proportional increase in IL-2 expression after OKT3 activation in CD4+ and CD8+ cells compared with patients on 100 mg. Moreover, some stop second generation TKI trials have mentioned that lower CD4+ T cells count before discontinuation was a significant favorable prognostic factor for TFR, while a rise in the subset of effector memory CD8+ cells predicted molecular relapse [14, 20].

In our study, we failed to find the significant differences of total T cells, CD4+ or CD8+ T cells between the recurrence and successful TFR groups, illustrating that NK cells-mediated immune response may play a key role in this study. The contribution of the leukemic stem cell activation and the immune system clearly requires further study and whether increased periods of de-escalation could mitigate the sharp fall in recurrence-free survival after subsequent cessation will be interesting to investigate.

The data on the HRQOL of patients during TFR are still limited. Several studies [24–26] evaluating TFR show stable or improved HRQOL after TKI discontinuation, but 20%–30% of patients manifesting as
increased musculoskeletal pain after stopping therapy, little is known about the emotional impact of attempting TFR. Therefore, we used EORTC QLQ-C30 questionnaire to assess HRQOL in the de-escalation and discontinuation groups. We found that most functional scales and symptoms were similar in these two groups. But regarding the emotional functioning, TKIs-off patients tend to be more serious, this may be explained by patients’ fear of relapsing after cessation, reminding us to pay more attention to patients’ mental health when stopping the TKIs. Fatigue and pain consisting of TKIs withdrawal syndrome were significantly worsened in the discontinuation group ($P = 0.024$ and 0.03, respectively), as discovered by Park et al. [25]. And more patients complained newly developed musculoskeletal pain after TKIs’ cessation ($P = 0.021$). Since patients who relapsed would spend more to restart medication and monitor the disease frequently, financial difficulties were more common in the discontinuation group ($P = 0.036$).

In summary, we present data that de-escalation may improve the proportion of patients in stable MMR for patients who achieved DMR, immune reconstitution maybe one of the mechanisms. Compared with abruptly discontinuation, the de-escalation group showed better disease-specific HRQOL. Our results support the rationale for TKI dose de-escalation in patients who have already reached sustained remission.

ACKNOWLEDGMENT
Jie Luo and Xin Du contributed equally to this work should be considered as co-first authors.

CONFLICT OF INTEREST
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are not publicly available due to privacy or ethical restrictions.
ETHICS STATEMENT
Ethics committee consent was obtained prior to the study.

PATIENT CONSENT STATEMENT
We have obtained written informed consent or verbal consent from the patient or patient’s parent/guardian already.

REFERENCES
1. Hochhaus A, Baccarani M, Silver RT, Schiffer C, Apperley JF, Cervantes F, et al. European Leukemia Net 2020 recommendations for treating chronic myeloid leukemia[J]. Leukemia. 2020;34(4):966–84.
2. Nasser A, Hussein A, Chamba C, Yonazi M, Mushli R, Schuh A, et al. Molecular response to imatinib in patients with chronic myeloid leukemia in Tanzania[J]. Blood Adv. 2021;5(5):1403–11.
3. Mahon FX. Treatment-free remission in CML: Who, how, and why? J Hematology Am Soc Hematol Educ Program. 2017;2017(1):102–9.
4. Clark RE. Tyrosine kinase inhibitor therapy discontinuation for patients with chronic myeloid leukemia in clinical practice. J Curr Hematol Malig Rep. 2019;14(6):507–14.
5. Kunbaz A, Eskazan AE. An alternative way— Tyrosine kinase inhibitor (TKI) de-escalation—To discontinue TKIs in order to achieve treatment-free remission. J Expert Rev Hematol. 2019;12:477–80.
6. Sharf G, Marin C, Bradley JA, Bomback F, Christensen RO, Gouimi B, et al. Treatment-free remission in chronic myeloid leukemia: The patient perspective and areas of unmet needs. J Leukemia. 2020;34(8):2102–12.
7. Iurlo A, Cattaneo D, Bucelli C, Breccia M. Dose optimization of tyrosine kinase inhibitors in chronic myeloid leukemia: A new therapeutic challenge. J Clin Med. 2021;10(3):515.
8. Clark RE, Polydoros F, Apperley JF, Milojkovic D, Rothwell K, Pocock C, et al. De-escalation of tyrosine kinase inhibitor dose in patients with chronic myeloid leukemia with stable major molecular response (DESTINY): An interim analysis of a non-randomised, phase 2 trial. J Lancet Haematol. 2017;4(7):e310–6.
9. Clark RE, Polydoros F, Apperley JF, et al. De-escalation of tyrosine kinase inhibitor therapy before complete treatment discontinuation in patients with chronic myeloid leukemia (DESTINY): A non-randomised, phase 2 trial. J Lancet Haematol. 2019;6(7):e375–83.
10. Austin GM, Knight K, Bell J, Carter A, Heartin E, Watson D, et al. The effect on lymphocyte subsets of decreasing/stopping tyrosine kinase inhibitor therapy in chronic myeloid leukemia: data from the DESTINY trial. Br J Haematol. 2019;185(4):791–3.
11. Fassoni AC, Baldow C, Roeder I, Glauche I. Reduced tyrosine kinase inhibitor dose is predicted to be as effective as standard dose in chronic myeloid leukemia: A simulation study based on phase III trial data. Haematologica. 2018;103(11):1825–34.
12. Muselli F, Peyron JF, Mary D. Druggable biochemical pathways and potential therapeutic alternatives to target leukemic stem cells and eliminate the residual disease in chronic myeloid leukemia. Int J Mol Sci. 2019;20(22):5616.
13. Irani YD, Hughes A, Clarson J, Kok C, Shanmuganathan N, White DL, et al. Successful treatment-free remission in chronic myeloid leukemia and its association with reduced immune suppressors and increased natural killer cells. Br J Haematol. 2020;191(3):433–41.
14. Cayssials E, Jacomet F, Piccirilli N, Lefèvre L, Roy L, Guilhot F, et al. Sustained treatment-free remission in chronic myeloid leukemia is associated with an increased frequency of innate CD8(+) T-cells. Br J Haematol. 2019;186(1):54–9.
15. Ryoo BY, Merle P, Kulkarni AS, et al. Health-related quality-of-life impact of pembrolizumab versus best supportive care in previously systemically treated patients with advanced hepatocellular carcinoma: KEYNOTE-240. Cancer. 2021;127(6):865–74.
16. Russo D, Garcia-Gutierrez JV, Soverini S, Baccarani M. Chronic myeloid leukemia prognosis and therapy: Criticisms and perspectives. J Clin Med. 2020; 9(6):1709.
17. Saussele S, Richter J, Guilhot J, Gruber FX, Hjorth-Hansen H, Almeida A, et al. Discontinuation of tyrosine kinase inhibitor therapy in chronic myeloid leukemia (EURO-SKI): A prespecified interim analysis of a prospective, multicentre, non-randomised, trial. Lancet Oncol. 2018;19(6):747–57.
18. Nicolini FE, Dulucq S, Bourleau L, Cony-Makhoul P, Charbonnier A, Escoffre-Barbe M, et al. Evaluation of residual disease and TKI duration are critical predictive factors for molecular recurrence after stopping imatinib first-line in chronic phase CML patients. Clin Cancer Res. 2019;25(22):6606–13.
19. Fava C, Rege-Cambrin D, Dogliotti I, Cerrano M, Berchilla P, Dragani M, et al. Observational study of chronic myeloid leukemia Italian patients who discontinued tyrosine kinase inhibitors in clinical practice. Haematologica. 2019;104(8):1589–96.
20. Kimura S, Imagawa J, Murai K, Hino M, Kitawaki T, Okada M, et al. Treatment-free remission after first-line dasatinib discontinuation in patients with chronic myeloid leukemia (first-line DADI trial): A single-arm, multicentre, phase 2 trial. Lancet Haematol. 2020;7(3):e218–25.
21. Alves R, Mcardle S, Vadakekolathu J, Gonçalves AC, Freitas-Tavares P, Pereira A, et al. Flow cytometry and targeted immune transcriptomics identify distinct profiles in patients with chronic myeloid leukemia receiving tyrosine kinase inhibitors with or without interferon-α. J Transl Med. 2020;18(1):2.
22. Rea D, Henry G, Khaznadar Z, Etiennë G, Guilhot F, Nicolini F, et al. Natural killer-cell counts are associated with molecular relapse-free survival after imatinib discontinuation in chronic myeloid leukemia: The IMMUNOSTIM study. Haematologica. 2017;102(8):1368–77.
23. Harrington P, Dillon R, Radia DH, McLornan DP, Rousselot P, Rezvani K, et al. Inhibition of immune cell subsets is differentially affected by dasatinib dosage in patients with chronic phase CML. Blood. 2020;136.
24. Malagola M, Iurlo A, Abruzzese E, Bonifacio M, Stagno F, Binotto G, et al. Molecular response and quality of life in chronic myeloid leukemia patients treated with intermittent TKIs: First interim analysis of OPTkIMA study. Cancer Med. 2021;10(5):1726–37.
25. Park JS, Lee SE, Jeong E-J, Choi M-Y, Kim H-J, et al. Change in immune cell populations during TKI de-escalation—To discontinue TKIs in order to achieve treatment-free remission in chronic myeloid leukemia patients who discontinued tyrosine kinase inhibitors in clinical practice. Leuk Lymphoma. 2016;57(2):341–51.
26. Erçalı¸skan A, Seyhan ED, E¸skazan AE. Current evidence on the efficacy and safety of generic imatinib in CML and the impact of generics on health care costs. Blood Adv. 2021;5(17):3344–53.

How to cite this article: Luo J, Du X, Lou J, Wu J, Ma L, Huang J, et al. De-escalation or discontinuation of tyrosine kinase inhibitor patients with chronic myeloid leukemia: A multicentric, open-label, prospective trial in China. eJHaem. 2022;3:1220–1230. https://doi.org/10.1002/jha.2550