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Clinical efficacy and safety of imatinib treatment in children and adolescents with chronic myeloid leukemia

A single-center experience in China

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Abstract

Chronic myeloid leukemia (CML) is relatively rare in childhood and few studies have reported the clinical use of imatinib (IM) in pediatric CML. In this study, we evaluated the efficacy and tolerability of IM in children and adolescents with CML.

We investigated 21 patients under 18 years of age with newly diagnosed CML and treated with IM in Children's Hospital of Chongqing Medical University between May 2014 and February 2018. The disease was staged according to the European LeukemiaNet criteria and the IM dose was determined based on the disease stage. Cumulative responses and survival probabilities were estimated according to the Kaplan–Meier method.

The estimated complete hematologic response rate of chronic phase-chronic myeloid leukemia (CML-CP) was 89.5% at 3 months. The complete cytogenetic response rates increased with time, reaching 47.4%, 73.7%, and 80.3% at 6, 12, and 24 months, respectively. The cumulative major molecular response rates were 42.1% and 76.3% at 12 and 24 months, respectively. With a median follow-up time of 33.8 months (range, 3.2–61.7 months), the estimated 2-year overall survival (OS) rate for CML was 95.2% (95% confidence interval [CI], 70.7%–99.3%). None of the CML-CP patients progressed to the accelerated phase or had a blast crisis. The 2-year OS and progression-free survival rates for the CML-CP cohort were both 100%, while the estimated 2-year event-free survival rate was 68% (95% CI, 42.1%–84.2%). None of the patients in this group had treatment-related deaths or IM discontinuation due to drug toxicities, and only 1 patient had a grade III–IV nonhematologic adverse event. Overall, anemia was the most common adverse effect and 42.9% of patients had a decrease in bone mineral density.

IM was effective and the adverse effects were well-tolerated throughout the follow-up period in Chinese CML patients under 18 years of age.

Abbreviations: AML = acute myelogenous leukemia, BMD = bone mineral density, CCyR = complete cytogenetic response, CHR = complete hematologic response, CI = confidence interval, CML = chronic myeloid leukemia, CML-BC = blast crisis-chronic myeloid leukemia, CML-CP = chronic phase-chronic myeloid leukemia, EFS = event-free survival, ELN = European LeukemiaNet, FDA = Food and Drug Administration, HSCT = hematopoietic stem cell transplantation, IM = imatinib, IS = international scale, MMR = major molecular response, OS = overall survival, PCR = polymerase chain reaction, PFS = progression-free survival, Ph+ = Philadelphia chromosome-positive, TKI = tyrosine kinase inhibitor.

Keywords: adolescent, adverse effect, children, chronic myeloid leukemia, efficacy, imatinib

1. Introduction

Chronic myeloid leukemia (CML) is relatively rare in childhood, accounting for 2% of leukemia in children under 15 years of age, and 9% of leukemia in adolescents between 15 and 19 years of age.[1] The incidence is 1 and 2.2 million per year in these 2 age groups, respectively.[1] Due to the low incidence of CML and the lack of clinical research-based evidence, treatment of pediatric

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CML follows adult guidelines and the efficacy of these treatments in children and adolescents has been poorly investigated.[1] Imatinib (IM) is a small molecule tyrosine kinase inhibitor (TKI) which halts the proliferation and growth of tumor cells by selectively inhibiting BCR-ABL1 tyrosine kinase.[2] The US Food and Drug Administration (FDA) approved IM for adult CML in May 2001, and based on its efficacy in adults, IM was subsequently approved by the US FDA for CML patients under 18 years of age in 2003.[3] However, there are obvious differences in CML between children/adolescents and adults in terms of disease manifestation and progression,[1] and it is not necessarily prudent to treat children/adolescents following guidelines established for adults.

The application of IM has completely transformed CML, including in children and adolescent patients, from a fatal to a chronic disease.[4] A population-based study in the United Kingdom showed that complete and sustained remissions of CML in children and adolescents increased from approximately 10% to 80% with the introduction of hematopoietic stem cell transplantation (HSCT) and the subsequent advent of TKIs.[4] Although second-generation TKIs have been shown to be more potent and able to overcome most IM-resistance mutations in adults,[5,6] IM was the only TKI approved for the treatment of children and adolescents with CML by the end of 2017. Until now, few studies have reported the efficacy and safety of IM in pediatric CML.[7–9] In China, the clinical use of IM in children and adolescents began relatively late and reports are therefore even more limited.[10] It is therefore of great clinical value to investigate the use of IM in Chinese children and adolescents with CML. We report on the results from the largest children's specialist medical center in western China (the Children's Hospital of Chongqing Medical University), with the aim of evaluating the clinical efficacy and safety of IM in Chinese children and adolescents with CML.

2. Patients and methods

2.1. Study design

The study procedure was reviewed and approved by the Ethics Committee of the Children's Hospital of Chongqing Medical University (File No. 2019227). We investigated 21 patients under 18 years of age with newly diagnosed CML who were treated with IM in the Department of Hematology and Oncology of the Children's Hospital of Chongqing Medical University from May 2014 to February 2018, and retrospectively analyzed the safety and efficacy of the treatment in this cohort. The inclusion criteria were as follows:

(1) 0 to 18 years of age; and
(2) diagnosed with Philadelphia chromosome-positive (Ph+) or *BCR-ABL1* fusion gene-positive CML.

The exclusion criteria were as follows:

(1) additional cancers or immunodeficiency disease;
(2) received other anti-leukemia treatment (except hydroxyurea) before IM; and
(3) renal and liver function test results more than twice the upper normal range.

IM dosage was determined based on disease stage according to the European LeukemiaNet (ELN) criteria.[11] Patients in chronic phase received 260 to 300 mg/m^2/d of IM (maximum absolute dose = 400 mg), patients in accelerated phase received 400 mg/m^2/d (maximum absolute dose = 600 mg), and patients in blastic phase received 500 mg/m^2/d (maximum absolute dose = 800 mg). Short-term hydroxyurea (20–40 mg/m^2/d) was allowed before IM for all patients. Short-term induction chemotherapy for acute lymphoblastic leukemia or acute myelogenous leukemia (AML) was permitted in blastic phase patients before IM.

Patients who failed to meet the optimal response milestones by the ELN criteria[11] (defined as BCR-ABL1 $\leq$10% and/or Ph+ $\leq$35% at 3 months, BCR-ABL1 <1% and/or Ph+ = 0 at 6 months, or BCR-ABL1 $\leq$0.1% at 12 months or at any time) were allowed to increase the IM dosage, switch to a second-generation TKI, or undergo HSCT. Patients who discontinued IM for any reason were excluded from the study and were only observed for disease progression (accelerated phase or blastic phase) and survival. Patients who experienced grade III–IV toxicity were allowed to suspend IM for a short time or reduce the IM dosage.

2.2. Efficacy evaluation

Hematologic responses were assessed by routine blood tests every 1 to 2 weeks after initiation of IM until complete hematologic response (CHR), and every 3 months thereafter. Cytogenetic and molecular responses were evaluated 3, 6, and 12 months (±1 months) after commencement of IM treatment. If a major molecular response (MMR) was achieved, the responses were evaluated every 6 months thereafter; if MMR was lost or not achieved, the responses were evaluated every 3 months thereafter. Cytogenetic analysis was performed in bone marrow metaphase cells by chromosome G-banding analysis (only samples with at least 20 metaphases were considered evaluable). Fluorescence in situ hybridization was used as an alternative in patients with insufficient metaphase cells. Molecular analysis of BCR-ABL1 transcription levels in bone marrow mononuclear cells was assessed by quantitative polymerase chain reaction (PCR). The *BCR-ABL1* gene assay obtained an International Scale (IS) conversion factor of 0.74. Mutation monitoring of the ABL1 kinase region was performed by nested PCR combined with sequencing assays when treatment failure occurred.

The efficacy of IM was measured according to ELN criteria.[11] CHR was defined as a leukocyte count $<10 \times 10^9$/L, platelet count $<450 \times 10^9$/L, basophils <5%, absence of myelocytes, promyelocytes, and blasts in the peripheral blood, and a non-palpable spleen. Complete cytogenetic response (CCyR) was defined as the absence of Ph+ cells. MMR was defined as a BCR-ABL1 IS $\leq$0.1%.

2.3. Safety evaluation

IM safety was assessed according to the National Cancer Institute common terminology criteria (version 3.0). Bone mineral density (BMD) was evaluated by dual-energy X-ray absorptiometry every 6 months and a $Z < -2.0$ was defined as decreased BMD.

2.4. End points

The primary end point of this study was the MMR response rate at 12 months. The secondary endpoints were overall survival (OS), progression-free survival (PFS), event-free survival (EFS), and safety of IM. OS time was defined as the time from diagnosis to death due to any cause or the last follow-up evaluation. PFS was considered as the time from the initiation of treatment to progression to accelerated phase or blastic phase, death, or the

last follow-up evaluation. EFS was measured from the start of IM to the date of any of the following events: death from any cause during treatment; progression to the accelerated phase or blastic phase; failure of treatment; treatment discontinuation for any reason; or the last follow-up. Failure was defined as no CHR and/or a Ph+ >95% at 3 months of treatment, a BCR-ABL1 >10% and/or a Ph+ >35% at 6 months treatment, a BCR-ABL1 >1% and/or a Ph+ >0 at 12 months treatment, loss of existing CHR or CCyR or MMR, or clonal chromosome abnormalities in Ph+ cells or a ABL1 kinase region mutation.

2.5. Statistical analysis

Cumulative responses (CHR, CCyR, and MMR) and survival probabilities (OS, PFS, and EFS) were estimated using the Kaplan–Meier method. To evaluate the efficacy of IM, patients who discontinued IM for any reason without achieving treatment responses were considered as no response instead of being censored. All statistical analyses were performed with GraphPad Prism 7.0 software.

3. Results

3.1. Patients and treatment

Twenty-one children and adolescents with CML were investigated in the study, including 13 males and 8 females. The median age at the time of CML diagnosis was 9.9 years (range, 5.9–15.3 years). Nineteen patients had chronic phase-chronic myeloid leukemia (CML-CP) and 2 had blast crisis-chronic myeloid leukemia (CML-BC). One patient was excluded from the statistical analysis because of treatment abandonment after diagnosis. The baseline clinical data are shown in Table 1.

All patients received short-term hydroxyurea treatment before IM for a median time of 19 days (range, 4–52 days). The median time from diagnosis to initiation of IM was 6 days (range, 0–44 days). The median initial dose of IM in the CML-CP cohort was 285.7 mg/m^2·d (range, 240.0–396.0 mg/m^2·d). During treatment, 7 of 19 (36.8%) CML-CP patients increased the IM dose to 341.9 mg/m^2·d (range, 312.5–396.0 mg/m^2·d) due to the lack of optimal response with the standard dose or loss of the achieved molecular response. The median time from initiation of IM to the increased IM dose was 4.9 months (range, 2.9–6.8 months). One patient in blastic phase was treated with IM at a dose of 370.4 mg/m^2 after receiving short-term AML-induced remission chemotherapy. Another blastic phase patient was treated with an initial IM dose of 204.7 mg/m^2 due to severe thrombocytopenia. The treatment of this cohort is shown in Figure 1.

Table 1

Baseline demographic and clinical characteristics of pediatric chronic myeloid leukemia (n = 21).

Clinical features	M/n	Range/%
Age, yr	9.9	5.9–15.3
Sex (male/female)	13/8	61.9%/38.1%
White blood cell count, $\times 10^9$/L	318.8	69.9–657.8
Platelet count, $\times 10^9$/L	384	115–960
Hemoglobin, g/L	86	65–129
Spleen size, below the costal margin, cm	13.5	0–25.5
Stage (chronic/accelerated/blastic)	19/0/2	90.5%/0/9.5%
Follow-up duration, mo	33.8	3.2–61.7
Sokal risk score* (low/intermediate/high)	9/9/3	42.9%/42.9%/14.3%

* Sokal risk score = Exp (0.0116 [age − 43.4]) + 0.0345 (spleen − 7.51) + 0.188 ([platelets/700]^2 − 0.563) + 0.0887 (blasts − 2.1); low, <0.8; intermediate, 0.8–1.2; high, >1.2.

3.2. Efficacy

3.2.1. Hematologic, cytogenetic, and molecular responses.

In the CML-CP cohort, 18 of 19 (94.7%) patients achieved a CHR by the end of the follow-up period. After 3 months of IM treatment, 17 of 19 (89.5%) patients achieved a CHR, while 2 of 19 (10.5%) patients failed to achieve a CHR (palpable spleen, n = 2). The cumulative incidences of CHR in CML-CP patients were 89.5% and 94.7% at 3 and 12 months, respectively (Fig. 2). In the CML-BC cohort, 1 of 2 patients achieved a CHR by 3 months.

In the CML-CP cohort, 13 of 19 (68.4%) patients achieved a CCyR by 12 months (Table 2), and 1 patient achieved a CCyR after 12 months. The CCyR rates increased with time, reaching 47.4%, 73.7%, and 80.3% at 6, 12, and 24 months, respectively (Fig. 2). During the follow-up period, 1 patient lost the CCyR at 17.8 months after the initiation of IM. In the CML-BC cohort, 1 of the 2 patients achieved a major cytogenetic response (Ph+ ≤35%) at 3 months, while the other patient had no cytogenetic response (Ph+ >95%).

In the CML-CP cohort, a MMR at 12 months was observed in 10 of 19 (52.6%) patients (Table 2), while 3 patients achieved a MMR after 12 months. Overall, the cumulative incidences of MMR were 42.1% and 76.3% at 12 and 24 months, respectively (Fig. 2). During the follow-up period, 3 patients reached a molecular response[4,7] (defined as a BCR-ABL1 IS ≤0.002%). Two patients lost the MMR at 10.1 and 17.8 months after the initiation of IM, respectively. In the CML-BC cohort, 1 patient had a BCR-ABL1 IS ≤10% by 3 months and another patient had a BCR-ABL1 IS >10%.

3.2.2. Survival. In the CML-CP cohort, 13 of 19 (68.4%) patients remained on IM by the end of the follow-up period (Fig. 1). Of the 19 patients, 6 (31.6%) discontinued IM treatment; 2 patients failed to achieve MMR at 13.2 and 15.6 months, 1 patient had a Ph+ >65% after treatment for 7 months, 1 patient with central infiltration did not achieve a CCyR after 7.9 months of treatment, 1 patient experienced a CCyR loss after 17.8 months of treatment, and 1 experienced a MMR loss after 10.1 months of treatment. There was no *ABL1* gene mutation in any of the above patients. All of the above patients who discontinued IM were switched to dasatinib (Fig. 1), and the median duration of IM treatment in this group was 11.7 months (range, 7–17.8 months). In the CML-BC cohort, 1 patient died of disease progression at 3.2 months after the initiation of IM, while the other patient remained alive (Fig. 1).

The follow-up period ended on June 1, 2019. With a median follow-up duration of 33.8 months (range, 3.2–61.7 months), the estimated 2-year OS rate of CML was 95.2% (95% confidence interval [CI], 70.7%–99.3%; Fig. 3A). Remarkably, none of the CML-CP patients progressed to accelerated phase or had a blast crisis. The estimated 2-year PFS and OS rates of CML-CP patients, including those who were switched to dasatinib, were both 100%. Overall, the estimated 2-year EFS was 68% (95% CI, 42.1%–84.2%; Fig. 3B).

3.3. Safety

Overall, the adverse effects in this cohort were mainly grade I or II (Table 3). There were no treatment-related deaths or IM

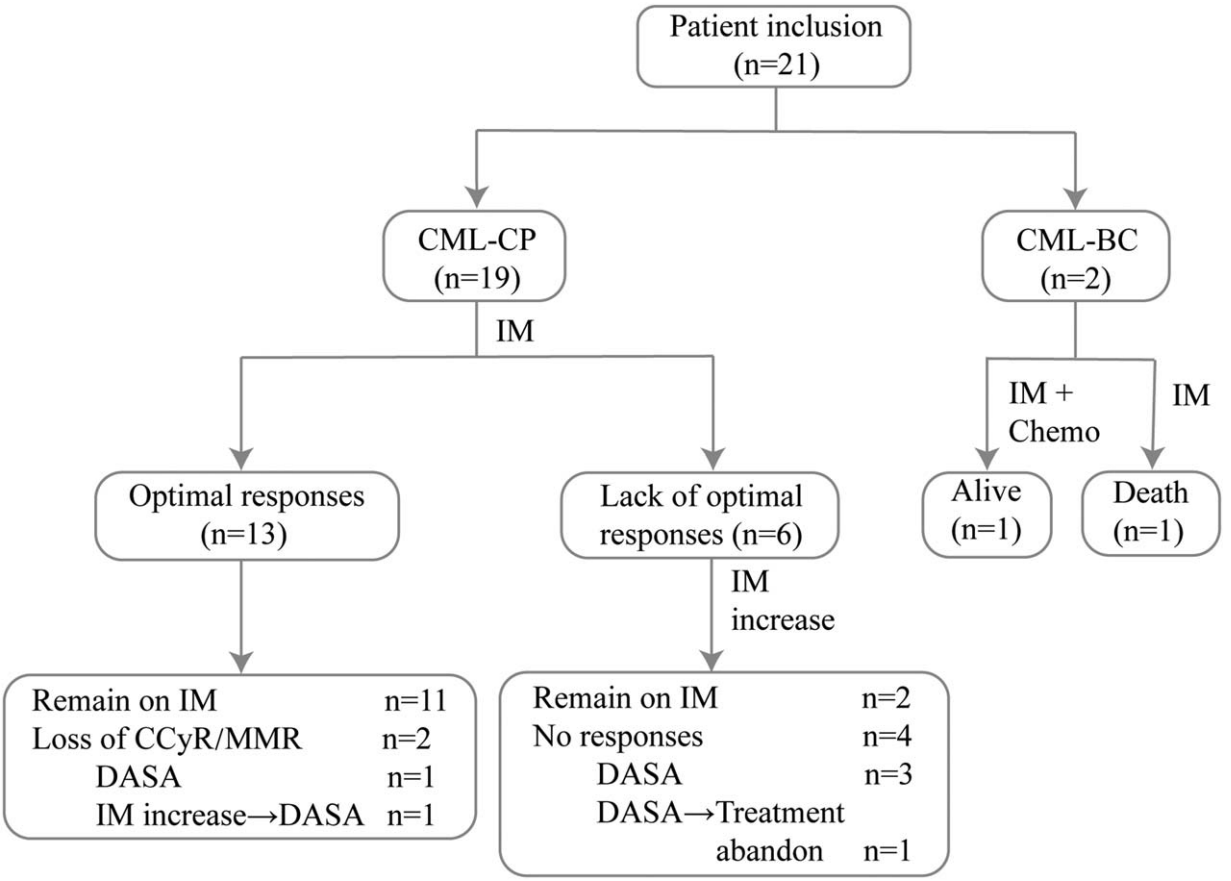

Figure 1. Flow chart of disease stage and treatment in patients with pediatric CML. CCyR = complete cytogenetic response, Chemo = chemotherapy, CML-BC = blast crisis-chronic myeloid leukemia, CML = chronic myeloid leukemia, CML-CP = chronic phase-chronic myeloid leukemia, DASA = dasatinib, IM = imatinib, MMR = major molecular response.

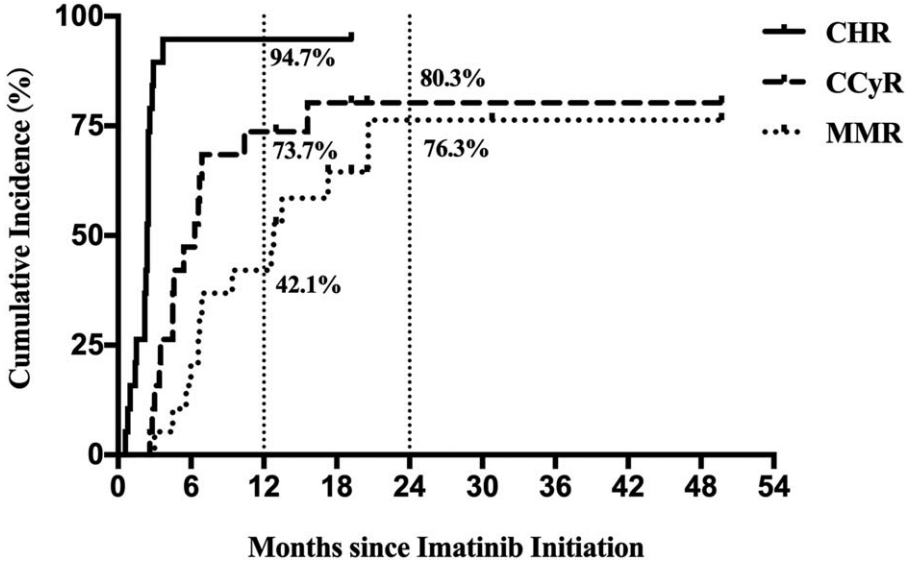

Figure 2. Cumulative incidence of CHR, CCyR, and MMR in children with CML-CP. The cumulative rates of CCyR were 47.4%, 73.7%, and 80.3% at 6, 12, and 24 months, respectively. The cumulative rates of MMR were 42.1% and 76.3% at 12 and 24 months, respectively. CHR = complete hematologic response, CML-CP = chronic phase-chronic myeloid leukemia, CCyR = complete cytogenetic response, MMR = major molecular response.

Table 2

Cytogenetic and molecular responses in children with chronic phase-chronic myeloid leukemia (n = 19[%]).

Response to treatment	3 mo	6 mo	12 mo
Cytogenetics response (Ph+)			
0	5 (26.3)	13 (68.4)	13 (68.4)
1%–35%	7 (36.8)	4 (21.1)	1 (5.3)
36%–65%	4 (21.1)	0	0
66%–95%	1 (5.3)	1 (5.3)	0
>95%	0	0	0
Unable to evaluate*	2 (10.5)	1 (5.3)	5 (26.3)
Molecular response (*BCR-ABL1* IS)			
≤ 0.1%	1 (5.3)	8 (42.1)	10 (52.6)
0.1%–1%	1 (5.3)	4 (21.1)	2 (10.5)
1%–10%	8 (42.1)	4 (21.1)	2 (10.5)
>10%	8 (42.1)	2 (10.5)	0
Unable to evaluate*	1 (5.3)	1 (5.3)	5 (26.3)

IS = international scale, Ph+ = Philadelphia chromosome-positive.
* Unable to evaluate includes patients in whom the treatment response was not evaluated at a certain period of time or who stopped imatinib treatment.

Table 3

Adverse effects in children with chronic myeloid leukemia undergoing imatinib treatment (n = 21).

Adverse effects	Grade I–II	Grade III–IV	All grades
Hematological adverse effects			
Anemia	15 (71.4)	4 (19.0)	19 (90.5)
Neutropenia	15 (71.4)	2 (9.5)	17 (81.0)
Thrombocytopenia	5 (23.8)	4 (19.0)	9 (42.8)
Gastrointestinal adverse effects			
Nausea	8 (38.1)	0	8 (38.1)
Vomiting	7 (33.3)	0	7 (33.3)
Diarrhea	2 (9.5)	0	2 (9.5)
Abdominal pain	1 (4.8)	0	1 (4.8)
Musculoskeletal adverse effects			
Muscle spasm	6 (28.6)	0	6 (28.6)
Bone or joint pain	3 (14.3)	1 (4.8)	4 (19.0)
Others			
Edema	8 (38.1)	0	8 (38.1)
Fatigue	2 (9.5)	0	2 (9.5)
Mammogenesis	1 (4.8)	0	1 (4.8)
Bone mineral density decreased	9 (42.9%)	0	9 (42.9%)

discontinuation due to drug toxicities. Only 1 patient experienced grade III–IV nonhematologic toxicity (bone and joint pain [grade III]). Anemia was the most common overall adverse effect. Hematologic adverse effects were mainly anemia and neutropenia. The most common non-hematologic adverse effects were gastrointestinal, followed by musculoskeletal. BMD decreased in 9 of 21 (42.9%) patients ($Z < -2.0$). Mammogenesis was observed in one 17-year-old boy.

4. Discussion

In recent years, the survival of patients with pediatric CML has significantly improved with the clinical application of TKIs. The therapeutic responses to TKIs at specific time points are important prognostic measurement indicators for CML patients and have been incorporated into global treatment guidelines.[11,12] The response criteria have been classified as optimal, warning, and failure according to hematologic, cytogenetic, and molecular indicators at 3, 6, and 12 months.[11] The optimal response is associated with the best long-term outcomes. Warning response requires close monitoring to ensure the timely detection of treatment failure. With respect to failure, patients should be switched promptly to other therapies to reduce the risk of disease progression and death. We evaluated the treatment response according to ELN criteria,[11] to obtain a more reliable clinical conclusion.

Previous international prospective multicenter studies of adult CML-CP showed the remarkable efficacy of a standard IM dose (400 mg/d), with CCyR and MMR rates of 65% to 73% and 27% to 50% at 12 months, respectively.[13–15] The treatment responses in previous pediatric studies differed from the current responses, possibly due the small sample sizes and differences in the IM dosages used. The CCyR and MMR rates were 61% to 96% and 31% to 67% at 12 months, respectively.[7–9] Our study was similar to most previous reports. IM was administered at 260 to 300 mg/m^2 (children's dose 260–340 mg/m^2 similar to an adult

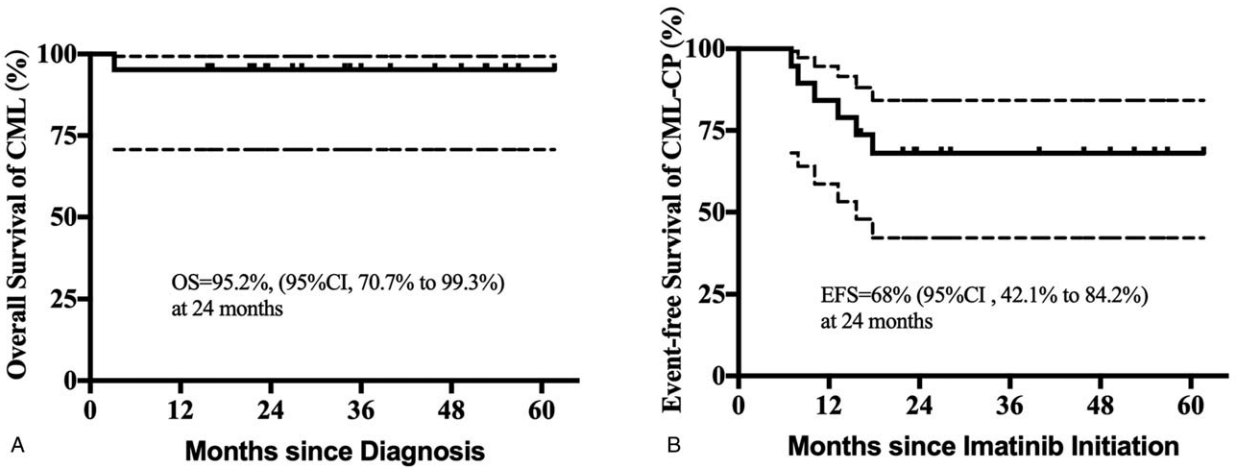

Figure 3. Survival rates of children with chronic myeloid leukemia. (A) The 2-yr OS rate of CML patients was 95.2% (95% CI, 70.7%–99.3%). (B) The 2-yr EFS rate of CML-CP patients was 68% (95% CI, 42.1%–84.2%). Dotted lines show the 95% CI. CI = confidence interval, CML = chronic myeloid leukemia, CML-CP = chronic phase-chronic myeloid leukemia, EFS = event-free survival, OS = overall survival.

dose 400–600 mg/d[3]) for CML-CP, and the CCyR and MMR rates at 12 months were 73.7% and 42.1%, respectively. The response rates reported in a Italian multicenter clinical study were better than those presented in our study and in other studies, which could be attributed to the higher IM dosage used (340 mg/m^2, similar to adult dose 600 mg/d).[7]

Patients in this study exhibited good medication compliance. Only one 11-year-old patient who failed to achieve MMR at 12 months had poor compliance. The adherence rate was approximately 50% within 4 months after initiating IM (no treatment for approximately 2 months). A CML study involving adults showed that adherence was an independent predictor of MMR.[16] Patients with a compliance rate ≥90% had a higher MMR rate at 6 years after treatment compared with those with a compliance rate <90% (95% vs 28%).[16] A report of Indian children with CML-CP highlighted the importance of compliance in the early treatment of IM due to the association with CCyR and long-term prognosis.[17] Adolescents generally show poorer adherence compared with the elderly and younger children,[1] suggesting that more attention should be focused on adolescents.

A phase IV clinical study reported that approximately 20% of patients received an increased IM dosage due to unsatisfactory responses to standard doses, but no better response rates were attributed to this dose escalation.[8] In the present study, the IM dose was increased in 36.8% of CML-CP patients who failed to achieve optimal responses or who lost their previously achieved molecular response, and the dose increase was only effective in 2 patients. Among the remaining 5 patients, dasatinib was effective in 2 patients after failure of the increase in IM dose. A phase II clinical study in adults showed that switching to dasatinib yielded a better treatment response and PFS compared with an increased dose of IM in patients who were resistant to IM.[18] Thus, switching to second-generation TKIs may be preferable to increasing doses in IM-resistant patients.

The estimated 2-year OS rate of CML patients in our study was 95.2%, which was similar to reports from a previous pediatric trial.[9] The OS and PFS rates of patients in the chronic phase were both 100% at 2 years, which were better than the 2-year OS (95%–96%) and PFS rates (92%–95%) reported in adult studies,[13,14] and the 18-month PFS rate (97%) in children.[9] In the present study, we switched to dasatinib relatively early when a patient exhibited treatment failure. We speculate that switching to dasatinib early may prevent disease progression to the accelerated phase or blastic phase, or even death. The effect of IM on OS and PFS in this group may have been overestimated. Previous studies involving adults and children have reported that IM was discontinued in approximately 30% of CML-CP patients due to IM resistance/intolerance or other causes.[8,9,19,20] Adult studies have shown that patients with CML-CP have a 5-year EFS of 65% to 71%.[21,22] In the present study, 31.6% of CML-CP patients discontinued IM, all within 2 years. The 2-year EFS of children with CML-CP was 68%. The main factors affecting EFS were treatment failure, followed by loss of the achieved molecular response.

The 10-year follow-up of the International Randomized Study of Interferon versus STI571 showed that 6.9% of patients discontinued IM due to severe adverse effects.[15] In studies involving children with CML-CP, 5% to 6% discontinued IM due to severe adverse effects.[8,9] No severe adverse effects were observed in the present study, possibly due to the small sample size. IM-related bone remodeling disorders and BMD changes have been reported in previous studies,[23,24] and varying degrees of growth restriction were observed in children.[9] We observed a reduced BMD in 42.9% of patients. Calcium and vitamin D supplementation were given to patients with low BMD, and extra calcitriol to patients with severely reduced BMD or bone pain. Although no significant recovery of BMD was observed, no patients had fractures. However, the effect of IM on growth could not be determined due to the relatively short follow-up period. Giona et al[24] observed elevated progesterone levels in 3 prepubertal male patients and 1 male had severe oligozoospermia after treatment with IM. We observed mammogenesis in a male patient. IM may affect hormone levels and responses in young people, but whether or not the long-term presence of these adverse effects impairs fertility is not clear.

In conclusion, we observed that IM produced a good treatment response as well as good survival rates, and was well-tolerated throughout the follow-up period in Chinese children with CML. However, the low incidence of pediatric CML means that the sample size in the present study was relatively small and the follow-up period relatively short. Further prospective multicenter trials are therefore needed to evaluate the efficacy and safety of IM and other second-generation TKIs.

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Author contributions

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Project administration: Jie Yu.
Supervision: Jie Yu.
Writing – original draft: Mengyue Deng.
Writing – review & editing: Jie Yu.

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