Long-term outcome of tyrosine kinase inhibitor treatment in children and adolescents with newly diagnosed chronic myeloid leukemia in chronic phase

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Chronic myeloid leukemia (CML) is relatively rare in children, with an average annual incidence of 0.6 to 1.0 case per million in children <15 years and 2.2 cases per million in adolescents aged 15 to 19 years, accounting for 2% to 3% and 9% of all newly diagnosed leukemia cases in these two age groups, respectively.[1] Imatinib mesylate (IM) was approved by the US Food and Drug Administration (FDA) in 2003 and has gradually replaced hematopoietic stem cell transplantation (HSCT) as the first-line treatment for pediatric patients with chronic-phase CML (CML-CP).[2] However, IM treatment is discontinued in 25% to 29% of pediatric patients with CML-CP because of drug resistance or intolerance.[3] For such patients, second-generation tyrosine kinase inhibitors (2G-TKIs), including dasatinib and nilotinib, were approved by the FDA as first- and second-line therapies in 2017 and 2018, respectively.[2] However, given the rarity of this neoplasm and the lack of clinical trial data, treatments for pediatric CML follow the recommended adult regimen, and little is known about the long-term efficacy and safety of these treatments in children and adolescents.[2] Furthermore, there are few reports detailing the sequential use of IM as first-line treatment followed by 2G-TKIs as second-line therapy in Chinese pediatric patients with CML. Therefore, there is a strong need to investigate the long-term effects of IM treatment in a large cohort of Chinese pediatric patients. In this report, we retrospectively analyzed the long-term follow-up results of 58 pediatric patients with CML-CP treated with IM as first-line therapy and 2G-TKIs as second-line therapy in a single South China center.

Patients were considered eligible if they were <18 years when diagnosed with Philadelphia chromosome-positive (Ph^+) CML-CP and were treated with IM as first-line therapy and 2G-TKIs as second-line therapy. The CML diagnosis and CP, accelerated phase (AP), and blast phase (BP) status at initial diagnosis were defined according to the European Leukemia Net (ELN) criteria.[4]

All patients with extremely high peripheral white blood cell counts were treated with short-term hydroxyurea (20–40 $mg \cdot m^{-2} \cdot day^{-1}$) before IM treatment. The initial IM dose was 260 to 300 $mg \cdot m^{-2} \cdot day^{-1}$ (maximum daily dose = 400 mg). Patients who experienced grade 3 to 4 toxicity received reduced IM doses or temporarily discontinued IM. If symptoms persisted, the patients were deemed IM-intolerant and switched to nilotinib or dasatinib. For patients who failed to reach the optimal response milestones,[4] the first recommendation was to increase the IM dose, followed by switching to a 2G-TKI and finally undergoing HSCT. The initial dose of dasatinib was 60 mg/m^2 once a day (maximum daily dose = 100 mg), and the initial dose of nilotinib was 230 mg/m^2 twice a day (maximum daily dose = 400 mg).

This study was approved by the Ethics Committee of our institution (Document No. 2020KY0111). Patients' parents or legal guardians provided informed consent in accordance with the *Declaration of Helsinki*.

Responses to TKIs were assessed according to the ELN criteria.[4] Complete hematologic response (CHR) was

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defined as normalization of peripheral blood counts and regression of hepatosplenomegaly. Complete cytogenetic response (CCyR) was defined as the absence of Ph^+ cells in the bone marrow (BM) metaphase. Major molecular response (MMR) was defined as $BCR\text{-}ABL1^{IS} \leq 0.1000\%$. Molecular response 4.0 ($MR^{4.0}$) was defined as $BCR\text{-}ABL1^{IS} \leq 0.0100\%$, and $MR^{4.5}$ was defined as $BCR\text{-}ABL1^{IS} \leq 0.0032\%$.

Overall survival (OS) was defined as the time from diagnosis to death from any cause or the last follow-up. Progression-free survival (PFS) was defined as the time from initial IM treatment to progression to AP or BP or death from any cause. Event-free survival (EFS) was defined as the time from initial IM treatment to the date of any of the following events: non-response to IM treatment, progression to AP/BP, or death from any cause. Failure of IM treatment was defined as the occurrence of any of the following events: no CHR and/or $Ph^+ > 95\%$ at 3 months from the beginning of treatment; $Ph^+ > 35\%$ and/or a $BCR\text{-}ABL1^{IS} > 10\%$ at 6 months from the beginning of treatment; BCR-ABL1 $> 1\%$ and/or $Ph^+ \geq 0\%$ at 12 months from the beginning of treatment; loss of CHR, CCyR, or MMR; occurrence of a new *ABL1* kinase domain (KD) mutation; or additional cytogenetic abnormalities in Ph^+ cells. The safety of TKIs was assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).

Differences in the proportions of variables between groups were compared using the Chi-square test or Fisher exact test. Cumulative response rates (CHR, CCyR, and MMR) and survival probability rates (OS, PFS, and EFS) were estimated using the Kaplan-Meier method. Patients who remained on TKI treatment were censored at the end of the follow-up period (May 30, 2020). The level of statistical significance was set at $P < 0.05$. All statistical analyses were performed using GraphPad Prism software (version 7.0; GraphPad Software, San Diego, CA, USA).

A total of 43 children and 15 adolescents with newly diagnosed CML-CP, 33 males and 25 females, were investigated in this study. The median age at CML-CP diagnosis was 10.2 years (range: 1.0–18.7 years). The clinical characteristics of the patients are presented in Supplementary Table 1, http://links.lww.com/CM9/A691.

Forty-five patients received short-term hydroxyurea as pre-IM cytoreductive treatment for a median duration of 14 days (range: 7–40 days). All patients were eligible for first-line IM treatment. The median interval between diagnosis and the beginning of IM administration was 10 days (range: 1–180 days). The median initial dose of IM was 280 $mg \cdot m^{-2} \cdot day^{-1}$ (range: 230–340 $mg \cdot m^{-2} \cdot day^{-1}$). In 26 patients, the IM dose was increased to a median dose of 330 $mg \cdot m^{-2} \cdot day^{-1}$ (range: 300–400 $mg \cdot m^{-2} \cdot day^{-1}$) due to a suboptimal response to the initial dose. For 17 patients, IM treatment was discontinued due to a lack of response after increasing the dose. One of the 17 patients received HSCT, and the other 16 patients switched to 2G-TKIs (eight patients to dasatinib and eight patients to nilotinib). Before 2G-TKI treatment, *ABL1* KD mutations were assessed using nested PCR in these 16 patients; one patient harbored the E255K mutation and one patient carried the Y253H mutation. The patient with the Y253H mutation optimally responded to the initial IM treatment and achieved MMR, then lost MMR and was switched to 2G-TKIs. Mutations in the *ABL1* KD were assessed again in six patients who progressed to the BP stage, and the T315I mutation was identified in two patients. The treatments and responses of this cohort are presented in Supplementary Figure 1, http://links.lww.com/CM9/A694.

After 3 months of IM treatment, 53 of 58 (91.4%) patients had achieved CHR, whereas four patients who had a leukocyte count $> 10 \times 10^9$/L and one patient who had a palpable spleen did not achieve CHR. All patients who achieved CHR did so within 7.0 months of initial IM administration. The median time to CHR was 2.5 months (range: 0.5–7.0 months). Six patients lost CHR at a median time of 33.3 months (range: 6.5–67.1 months) from initial IM treatment and progressed to CML-BP.

Of the 51 patients who received IM for >12 months, 88.2% (45/51) achieved major cytogenetic response, whereas 68.6% (35/51) achieved CCyR, based on BM cytogenetic analysis. The cumulative incidence of MMR at 12 months was 41.1% (21/51), and the cumulative incidence of $MR^{4.0}$ at 12 months was 27.5% (14/51). In the 47 patients who were administered IM for >18 months, the cumulative incidence of MMR was 66.0% (31/47). The cytogenetic and molecular responses to IM are listed in Supplementary Table 2, http://links.lww.com/CM9/A692.

When treated with IM, 36 patients (62.1%) achieved MMR in a median time of 12.1 months (range: 5.8–50.5 months). Among these 36 patients, 24 (41.4%) achieved $MR^{4.0}$, including 19 (32.8%) in whom the transcript level was below $MR^{4.5}$. In 16 patients who failed to respond to IM, 11 (68.8%) achieved MMR in a median time of 3.7 months (range: 3.0–26.0 months) after switching to dasatinib ($n = 6$) or nilotinib ($n = 5$). Among these 11 patients, 5 (31.3%) achieved $MR^{4.0}$ or less, including four patients (25%) who achieved $MR^{4.5}$. The cumulative incidences of MR, $MR^{4.0}$, and $MR^{4.5}$ in patients who received IM as first-line therapy and in those who switched to 2G-TKIs are shown in Supplementary Figure 2A and 2B, http://links.lww.com/CM9/A695, respectively. When the follow-up period ended on May 30, 2020, with a median follow-up of 44.8 months (range: 6.0–113.7 months), the 9-year OS rate was 81.1%, the 9-year PFS rate was 80.5%, and the 9-year EFS rate was 44.4% [Figure 1]. Twenty-four patients failed to respond to IM: 17 patients with no response and seven patients with molecular relapse. The median time from MMR to molecular relapse was 10.1 months (range: 3.1–37.5 months). One patient with molecular relapse received HSCT immediately, whereas the other six patients developed AP/BP progression, with a median time to progression of 34.6 months (range: 3.5–68.1 months). After disease progression, four patients did not undergo HSCT, and all died. Two patients received HSCT, one of whom died from HSCT-related complications. It should be noted that four adolescents (7%) had poor adherence to TKIs, frequently missing doses; two of them progressed to AP and the other two lost MMR.

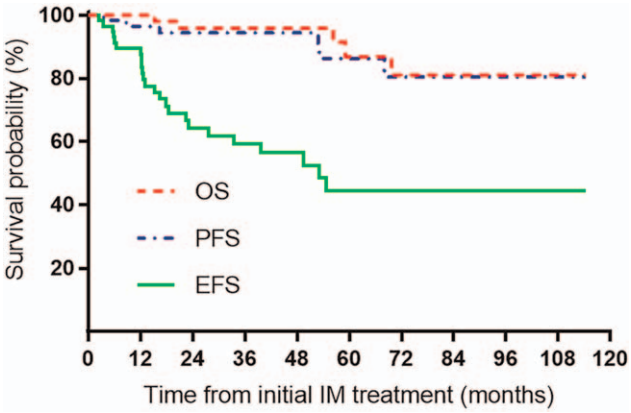

Figure 1: Survival rates of 43 children and 15 adolescents with chronic-phase CML. The 9-year OS was 81.1%. The 9-year PFS was 80.5%. The 9-year EFS was 44.4%. CML: Chronic myeloid leukemia; EFS: Event-free survival; IM: Imatinib mesylate; OS: Overall survival; PFS: Progression-free survival.

At a median time of 35.5 months (range: 6.1–114.3 months) into IM treatment, 38 patients (65.5%) experienced at least one adverse effect related to IM [Supplementary Table 3, http://links.lww.com/CM9/A693]. Most of the patients experienced grade 1 or 2 adverse effects within 6 months of IM initiation, among which the most common were anemia ($n = 36$, 62%) and gastrointestinal toxicity ($n = 20$, 34%). Nineteen patients (33%) experienced grade 3 or 4 hematological ($n = 15$, 26%) or extra-hematological ($n = 4$, 7%) adverse effects. Neutropenia ($n = 13$, 22%) and musculoskeletal pain ($n = 4$, 7%) were the most common grade 3 or 4 adverse events, and both led to either temporary treatment discontinuation or dose reduction. Nevertheless, there were no treatment-related deaths or permanent IM discontinuations. In 48 patients treated with IM longer than 12 months, 15 patients (31%) experienced longitudinal growth impairment. Of the 16 patients who switched to 2G-TKIs, only one experienced grade 3 events (pleural effusion and edema) at 1 month of dasatinib treatment.

In summary, we conclude that IM as first-line therapy and 2G-TKIs as second-line therapy for IM-intolerant/resistant patients resulted in a good early treatment response and drug tolerance in Chinese pediatric patients with CML-CP. Notably, poor treatment adherence remains a major problem in teenagers and is a common reason for treatment failure. Moreover, the rare incidence of pediatric CML resulted in the relatively small sample size of our study, and data on the long-term adverse effects of TKIs are very limited. Therefore, further prospective multicenter trials are needed to evaluate the efficacy and safety of IM and 2G-TKIs in Chinese pediatric patients with CML.

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Conflicts of interest

None.

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