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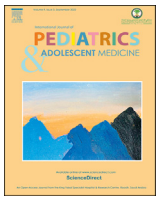

Original article

Outcome of pediatric chronic myeloid leukemia with management focusing on the monitoring of BCR-ABL fusion gene transcript levels

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ABSTRACT

Background and objective: Clinical, laboratory and outcome data were reviewed for pediatric patients who were diagnosed with chronic myeloid leukemia (CML) and managed at two tertiary care hospitals in Saudi Arabia, between January 2011 and December 2017 to assess the response to tyrosine kinase inhibitors (TKI) focusing on the monitoring of BCR-ABL fusion gene transcript levels and to look at the overall outcome.

Methods: CML patients were identified based on the cytogenetic and molecular results.

Results: Twelve pediatric patients diagnosed with CML at a median age of 8.4 year; treated with TKI as first-line therapy, 11 (91.7%) patients were started with imatinib (first-generation TKI), while one received dasatinib (second-generation TKI) due to his three-way Philadelphia chromosome sensitivity. Eight patients (72.7%) starting on imatinib were switched to dasatinib (six patients due to drug resistance, and two patients due to intolerance of Imatinib) and two patients (25%) of whom had already achieved major molecular response (MMR) on Imatinib. Response rate to imatinib in terms of achieving MMR as first-line therapy was achieved in five out of 11 patients (45.5%) and only three of them continued to maintain their MMR. Six out of eight patients who were switched to dasatinib achieved MMR. Two patients underwent hematopoietic stem cell transplant (SCT): one due to blast crisis and one due to the side effects of TKI. With a median follow-up time of 78 months (range, 40.5–108), all of our patients were alive at last update.

Conclusion: We report an excellent outcome with an overall survival (OS) of 100% at 5-year and disease-free survival (DFS) of 91.7% (8.0%). All our patients achieved MMR and only one patient had loss of MMR on follow-up. Eight patients (66.7%) achieved complete molecular response (CMR).

1. Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm characterized by dysregulated production and uncontrolled proliferation of granulocytes with normal differentiation. It is featured by a balanced translocation between chromosomes 9 and 22 t(9,22) (q34; q11), which results in the Philadelphia (Ph) chromosome and the fusion gene BCR-ABL [1]. CML is a very rare disease in children, accounting for less than 5% of childhood leukemia [2]. Clinically, CML can present in the chronic phase (CP), accelerated phase (AP), or blast phase (BP). In most cases, CML patients are diagnosed with CP, but about 10% of cases are diagnosed in the advanced phase (AP or BP) [3]. Forty percent of the patients diagnosed with CP are asymptomatic and may later progress from CP to AP and finally to BP. Although each phase's clinical and morphological boundaries may be blurred, the recognition of disease progression from CP to either AP or BP is important for both the treatment as well as overall prognosis of the patient [4]. The treatment objective is to decrease or eliminate the cells

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Abbreviations

CML-	Chronic Myeloid Leukemia
TKIT	yrosine Kinase Inhibitors
MMR	Major Molecular Response
SCTH	ematopoietic stem cell transplant
DFSD	disease-free survival
CMR	Complete Molecular Response
CPC	chronic phase
APA	Accelerated phase
BPB	last phase
RT-qPCR	Real-time quantitative reverse transcriptase-polymerase chain reaction
CHR	Complete Hematological Remission
CCyR	Complete Cytogenetic Response

with the abnormal Ph chromosome, which significantly improves cytogenetic response and shifts the blood counts to normal hematologic response [1]. The management of CML is based on the disease phase at presentation and response levels because these are measures of leukemic cell burden and early surrogate markers of survival. Real-time quantitative reverse transcriptase-polymerase chain reaction (RT-qPCR) is increasingly used for molecular monitoring of BCR-ABL transcript levels to assess the treatment response in patients with CML. In the last decade or so, RT-qPCR has become extremely important because of tyrosine kinase inhibitor (TKI's)-like imatinib therapy where residual levels of leukemia usually fall below the level of detection by bone marrow cytogenetic analysis [5].

Imatinib is a TKI for first-line treatment of CML [6]. Results from the studies of imatinib-treated patients have exhibited that BCR-ABL levels measured early in therapy can predict subsequent response and the probability of acquired resistance. The definition of a molecular-level response indicates a high probability of progression-free survival (PFS), which in turn signifies the relevance of molecular analysis for the clinical management of CML. Most of the data on imatinib mesylate therapy is derived from adult studies because CML is very rare in children. Imatinib is generally well-tolerated, and it certainly has very few side effects than conventional chemotherapy. Many patients may have hematologic toxicity as evidenced by cytopenia [2]. Imatinib has changed the prognosis for CML so dramatically that patients with newly diagnosed CML starting treatment with imatinib now have a normal life expectancy compared with the historical median survival of 2–3 years. Imatinib possesses a remarkably safe profile, in addition to its outstanding therapeutic activity [7]. We are reporting our experience of treating pediatric CML patients with TKI at XXX, and XXX, using identical treatment regimen.

2. Materials and methods

2.1. Patients

Twelve pediatric CML patients (age <14 years at diagnosis) diagnosed and treated at two tertiary care hospitals: XXX and XXX, consecutively between January 2011 and December 2017. All patients were identified based on the cytogenetic and molecular results and treated using National Comprehensive Cancer Network (NCCN) treatment protocol for pediatric CML. Clinical data including demographic characteristics, family history, and treatment outcomes were obtained through the review of medical records of the patients at the two treating centers.

2.2. Definitions

The diagnosis of CML was made according to the 4th edition of World Health Organization (WHO) classification of hematopoietic and lymphoid tissue. CP, AP, and BP were established using the mandatory molecular confirmation of BCR-ABL fusion [8,9]. The effectiveness of TKI therapy was evaluated based on milestones of the therapy achieved: Complete hematological remission (CHR) was defined as leukocyte count <10 x10^9/L, platelet <450 x10^9/L, absence of blasts in peripheral blood, and no splenomegaly [8]. After the patient achieves a complete cytogenetic response (CCyR), defined as BCR-ABL1 RT-qPCR of ≤1% (International Scale [IS]), monitoring via conventional bone marrow metaphase analysis provides minimal value. BCR-ABL1 RT-qPCR has limited value except at diagnosis and should be used to identify patients with atypical BCR-ABL1 transcripts. On the IS, results are expressed relative to the standardized baseline (for example, early molecular response (EMR) is defined as BCR-ABL1 (IS) ≤10%, major molecular response (MMR): BCR-ABL1 (IS) ≤0.1% or ≥3-log reduction, deep molecular response (DMR): BCR-ABL1 (IS) ≤0.0032%, and complete molecular response (CMR): BCR-ABL1 (IS) ≤0.001% or ≥4.5 log [10,11]. Any sign of loss of response (defined as hematologic or cytogenetic relapse) or 1-log decrease in BCR-ABL1 transcript levels with loss of MMR was considered as relapse [8,10].

Overall survival (OS) was defined as survival time in months from the date of diagnosis to last follow-up or death. Death from any cause was considered as an event. The loss of MMR or death was considered as an event for disease-free survival (DFS), whichever comes first. The last follow-up was performed in December 2020.

2.3. Data management and statistical analyses

IBM-SPSS version 20.0 (IBM, Armonk, USA) was used to collect, manage, and for the analysis of the data.

3. Results

3.1. Clinical presentation

Clinical characteristics of patients enrolled in this study are provided in Table 1. Seven (58.3%) patients were from KFSHRC and five (41.7%) from KFSH-D. The BCR-ABL1 major (p120) fusion forms were present in all the cases. There was a male predominance (n = 7, 58%). The median age at diagnosis was 8.4 years (range 0.8–13.5). At the time of diagnosis, majority of the patients were presented in the CP (n = 10, 83.3%), whereas two patients (16.7%) were presented in AP. None of the patients was in BP. All our patients presented with hyperleukocytosis, whereas eight (67%) had thrombocytosis, 11 (91.7%) had Ph chromosome positive, and one (8.0%) was with three-way Ph chromosome variant t(9; 22; 14). None of the patients had ABL kinase mutation.

3.2. Treatment and response

All patients were treated with TKIs as first-line therapy: 11 (91.7%) were stated on imatinib as the first-generation TKI, whereas one patient received dasatinib because of his 3-way Ph chromosome variant sensitivity. The response rate to imatinib as first-line therapy was 46% (5 of 11) in terms of achieving MMR. Eight patients (72.7%) who were started on imatinib were switched to dasatinib as second-line therapy (six because of drug resistance and two because of side effects and intolerance to imatinib). TKI-related toxicity and side effects by treatment agent are presented in Table 2.

The response rate to dasatinib in terms of achieving MMR was

Table 1
Demographics, clinical characteristics and hematological parameters at presentations (n = 12).

Characteristics of patients	Values in patients (%)
Age (years), median, range	8.4 (0.8–13.5) years
Gender	7 (58.3)
Male	7 (58.3)
Female	5 (41.7)
Distribution	
KFSHRC	7 (58.3)
KFSH-D	5 (41.7)
Symptoms	
Fever	6 (50)
Bone pain	4 (33.3)
Physical Findings	
Splenomegaly	12 (100.0)
Hepatomegaly	9 (75)
Lymphadenopathy	5 (41.7)
Hematological parameters	
WBC ($X10^9$/L)	193.0 (115.0–677.0)
Hemoglobin (g/dL)	9.0 (6.2–12.9)
Platelets ($X10^9$/L)	629.0 (126.0–970.0)
Peripheral Blasts	3.5 (1.0–19.0)
Peripheral Basophils	3.0 (1.0–28.0)
Bone marrow blasts	2.5 (1.0–10.0)

Values are in median (range) for continuous and n(%) for discrete variables.

75% (6 of 8). The two patients who were switched to dasatinib because of intolerance to imatinib maintained MMR; one patient continued on dasatinib, and the other one was switched to nilotinib after 28 months because of side effects of dasatinib and underwent SCT because of persistent side effects maintaining MMR (Fig. 1).

Four of the six patients who were switched to dasatinib because of resistance to imatinib maintained MMR; however, one of them was switched to nilotinib because of dasatinib side effects, whereas the remaining three were maintained on dasatinib. The other two patients lost the MMR; one patient developed blast crisis and later underwent SCT achieving MMR post-transplant, and the second one lost MMR because of non-compliance. The infant who received dasatinib as first-line therapy because of his three-way Ph chromosome variant sensitivity achieved MMR within 11 months from starting his treatment. At the most recent visit, his MMR was maintained, and his transcript level was undetectable. All our patients achieved CHR over a median of 3.0 months from the start of the TKI (range 1.5–9.4), EMR (median, 3.0 months, range, 1.6–18.7 months), CCyR (median,7.3 months, range, 2.2–42.9 months)m and MMR (median, 15.5 months, range 2.5–65.7 months); DMR was achieved in 10 (83.3%) patients over a median of 21.7 months (range 2.9–66.8 months), whereas CMR was achieved in 8 patients (66.7%) (median, 23.2 months, range 6.0–57.9 months).

3.3. Survival

With a median follow-up time of 78 months (range, 40.5–107.7), all our patients were alive at last contact. Five-year DFS of our small cohort of patients was 91.7% (8.0%) with only one event of loss of MMR (Fig. 2).

Table 2
Treatment side effects and toxicity.

	Imatinib (n = 11) 7 (63.6%)	Dasatinib (n = 9) 6 (66.7%)	Nilotinib (n = 2) 1 (50%)
Side effects			
Bone pain	3 (27.3)	2 (22.2)	–
GI bleeding	1 (9.1)	1 (11.1)	1 (50)
Skin rash	–	3 (33.3)	–
Toxicity			
Hematologic	2 (18.2)	2 (22.2)	–
Neurologic	2 (18.2)	–	–
Lymphadenopathy	1 (9.1)	1 (11.1)	–

4. Discussion

Our data support TKI as an effective treatment for long-term disease control with the adequate monitoring of BCR-ABL fusion gene transcript level, even without SCT. Of the two patients who underwent SCT, one had progression from accelerate phase to blast phase and other patient because of TKI side effect who achieved CMR before the transplantation. We report the follow-up regarding response in an infant who was the first case reported with three-way Philadelphia chromosome variant t(9; 22; 14) CML, by Al Hayek et al. [12]. He presented in the accelerated phase and was treated with dasatinib because of gene sensitivity. This infant showed good response, achieved MMR within 11 months after starting the treatment, and proceeded to have undetectable BCR-ABL levels. A study by Belgaumi et al. reports 12 pediatric CML patients treated at KFSHRC from 2003 to 2008. Of these, 50% of the patients were treated with imatinib, whereas the remaining underwent SCT; however, none of the patients receiving imatinib alone achieved CMR. In contrast to the SCT group, three of six patients had undetectable BCR-ABL, whereas other three patients relapsed (1 imatinib; 2 SCT) [13]. In our cohort, patients were treated with different TKI generations, and only two patients underwent SCT. All our patients achieved MMR, and then only one patient experienced loss of MMR, whereas eight patients (66.7%) achieved CMR, with a DFS of 91.7%.

Egan et al. reported their experience with the use of TKI monotherapy in childhood CML, showing decreased mortality in those who received and responded to imatinib. In their study, 52 patients were enrolled, and imatinib was well-tolerated and only discontinued in two patients secondary to refractory nausea and unexplained joint effusions [11]. In our group of patients (n = 11), there was variation in tolerance of imatinib, and switching to dasatinib was observed in only eight of 11 patients (72.7%). Of which, six patients (75%) were switched because of resistance and two (25%) because of side effects of imatinib after achieving MMR.

Furthermore, Tanizawa et al. stated that CML children with BCR-ABL $\leq$ 10% at 3 months after starting imatinib had higher rates of complete cytogenetic response and MMR at 12 months than those with BCR-ABL1 > 10%, highlighting 3 months' response (BCR-ABL1 <10% vs. >10%; OS 93% vs. 56%) as an important factor for the outcome [3,14–16]. All our patients achieved EMR (<10%) at a median of 3 months and MMR at a median of 15.5 months with excellent outcome and 100% OS. In a large cohort of 156 pediatric patients (age <18 years) treated with TKI (imatinib), 38 patients experienced imatinib failure because of unsatisfactory response (29 patients) or intolerance (9 patients) [7]. In addition, Kantarjian et al. reported the superiority of both dasatinib and nilotinib treatment in achieving both CCyR and MMR. However, it is still unknown whether this treatment translates into the superior long-term OS and PFS [3,15,17,18]. We could not compare imatinib with dasatinib as only one patient was initially started on dasatinib, and six patients were switched from imatinib to dasatinib because of resistance to imatinib. The MMR was achieved over a median of 12 months from the time of the switch, which supports the significance of using imatinib versus dasatinib as upfront therapy. As per the NCCN guidelines, the Stop Imatinib (STIM1) study looked at 100 patients who were in CMR for over 2 years on treatment with imatinib and stopped therapy. About 41% of the patients maintained CMR, despite not being on TKI therapy. Of those patients who relapsed and were re-challenged with imatinib, many regained CMR status [19,20]. However, some did not, and this remains a concern of discontinuing imatinib.

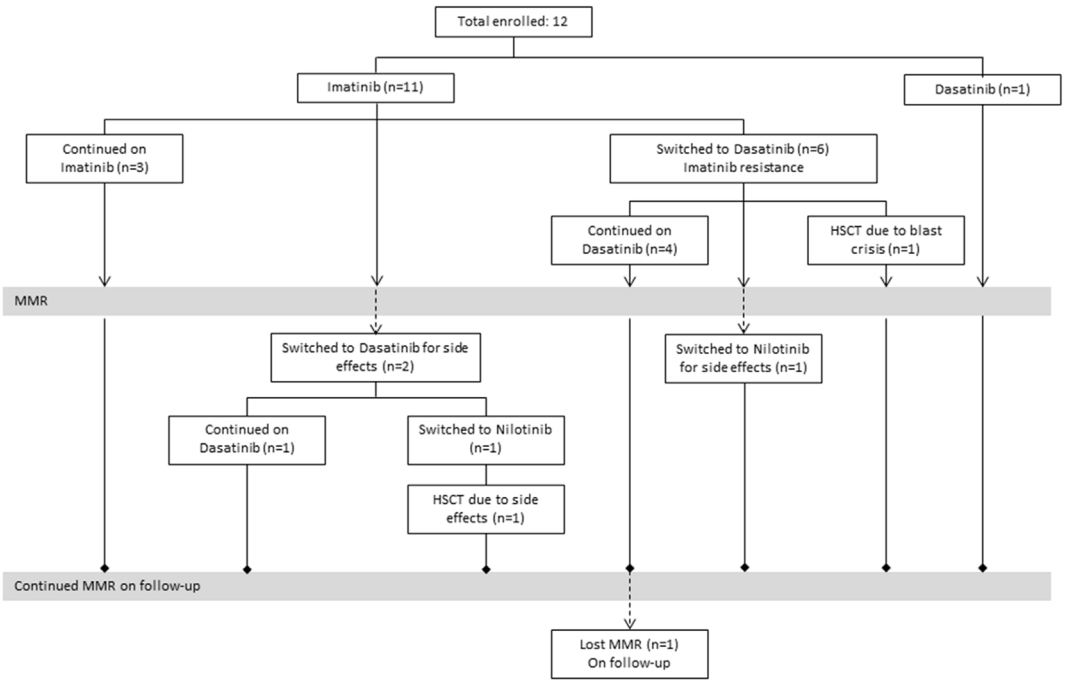

Fig. 1. Snapshot of the cohort by treatment and outcome.

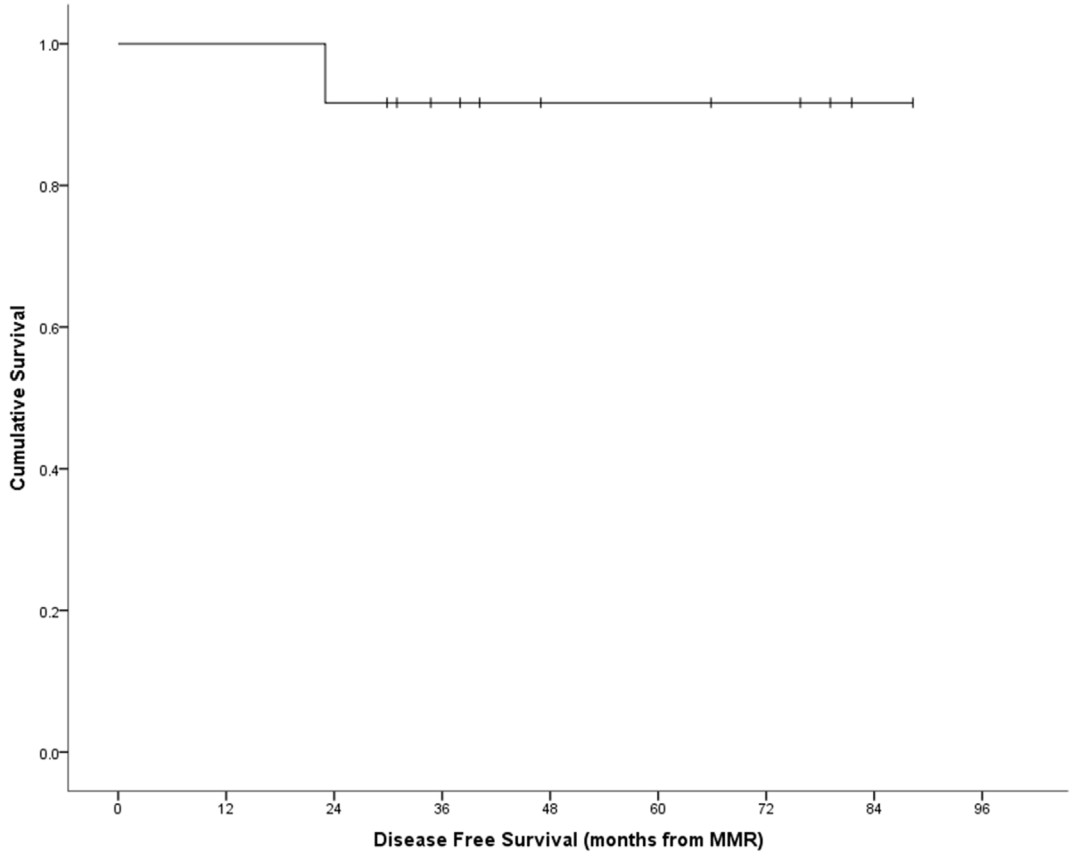

Fig. 2. Disease-free survival.

Costs should also be considered to judge the newer small molecule-based therapies. The price of imatinib and dasatinib is approximately US$ 31,983.50 (SAR 120,000) and US$ 50,640.53 (SAR 190,000) per year, respectively. However, a direct comparison of the two therapies is difficult because of confounding factors.

In conclusion, our series showed good outcome with OS of 100% and DFS of 91.7%, at a median follow-up of 78 months in pediatric CML treated with TKI. Patient compliance remains vital because

adherence to the proposed monitoring schedule will minimize delayed interventions. The early identification of patients who become resistant or intolerant to imatinib is critical in switching them to alternative TKI generation using the available tools for molecular testing. A larger cohort of children with CML is needed to determine the biological and clinical significance of comparing the different TKI generations in terms of which to be used upfront and to identify prognostic factors for survival and treatment failure in this age group.

Author statement

Ibrahim Ghemlas: Conceptualization; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Writing - original draft; Writing - review & editing. Saad Al-Daama: Conceptualization; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Writing - original draft; Writing - review & editing. Hawazin Aqueel: Conceptualization; Data collection; Investigation; Methodology; Validation; Writing - original draft; Writing - review & editing. Khawar Siddiqui: Data processing; Formal analysis; Methodology; Validation; Visualization; Writing - original draft; Writing - review & editing. Hassan ElSolh: Writing - review & editing. Hala Omer: Writing - review & editing. Loloah AlRajeh: Data collection; Investigation; Writing - review & editing. Amal AlSeraihy: Writing - review & editing. Ali AlAhmari: Writing - review & editing. Hawazen AlSaedi: Writing - review & editing. Awatif AlAnazi: Writing - review & editing. Mouhab Ayas: Validation; Writing - original draft; Writing - review & editing.

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Ethical approval

This clinical research study was approved by the Institutional Review Board (IRB) of both the hospitals via approval numbers 2191065 and EXT0343, which was to be conducted under the international guidelines for the enrollment of human subjects. The data from patients' medical records were collected and maintained in accordance with institutional policy on data confidentiality, security, and safety. As the study was designed as a retrospective review, no consent/assent was taken from patients/parents. A waiver of informed consent/assent was sought from the IRB and was duly granted.

Submission declaration and verification

The work described in this article has not been published previously (except in the form of an abstract, a published lecture, or academic thesis) and is not under consideration for publication elsewhere. Its publication is approved by all authors and is explicitly approved by the responsible authorities where the work was performed. If the work gets accepted for publication, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright holder.

Data statement

The data used in this work are available from the corresponding author upon reason request. However, some restrictions may apply.

Declaration of competing interest

The authors declare no conflicts of interest or competing interests.

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None.

Visual abstract

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijpam.2022.04.001.

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