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CML	Chronic Myeloid Leukemia
AP	Accelerated Phase
BP	Blast Phase
CP	Chronic Phase
HSCT	Hematopoietic Stem Cell Transplant
TKI	Tyrosine Kinase Inhibitor
WHO	World Health Organization

Abstract

Objective: Chronic myeloid leukemia (CML) is a rare disease in childhood. While hematopoietic stem cell transplant (HSCT) was the treatment of choice for CML prior to 2000, the introduction of tyrosine kinase inhibitors (TKIs) changed the management of this disease. . This population-based analysis was conducted in the province of Ontario, Canada to gather information on treatment choices and outcomes of childhood CML.

Method: Using a provincial childhood cancer registry and retrospective review of patient medical records for patients <18 years diagnosed with CML between 1985 and 2018, data on presenting features, treatment and outcomes was collected from 52 patients.

Results: Patients treated before the introduction of TKIs (<2002) mainly received HSCT and had an overall survival (OS) of 64% at a median follow up of 6 years. The OS of all patients treated in the TKI era (≥ 2002) was 90% at a median follow up of 3 years. All three deaths in the TKI era were related to HSCT complications. Survival of patients who remained on a TKI was significantly improved compared to those who underwent HSCT post TKI therapy (100% vs 66%, p = 0.008). TKIs were well tolerated.

Conclusion: Given the increased mortality associated with HSCT in our cohort, further advances in HSCT may be required to outweigh the benefits of a TKI mono-therapy approach in the majority of childhood CML patients. We believe HSCT should be considered in only a limited subset of pediatric patients with CML.

Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative disorder of hematopoietic stem cells that is rare in children, accounting for 2-3% of pediatric leukemias [1]. If untreated, CML progresses through 3 phases; the chronic phase (CP), the accelerated phase (AP), and the blast phase (BP); most patients present in the chronic phase. While allogeneic hematopoietic stem cell transplant (HSCT) was the treatment choice for CML prior to 2000,

the introduction of imatinib in the early 2000s changed the management of this disease.

Much of what is known about this disease and its therapy is based on studies of adult patients, with few clinical trials performed in pediatrics. The care of children with CML offers unique challenges. Compared with adults, children with CML are more likely to present with AP and BP disease and are less likely to achieve an early favorable molecular response [2,3]. Studies have suggested that there are differences in the biology of childhood CML, including variability in BCR-ABL1 breakpoints [4]. The safety and efficacy of imatinib in the treatment of childhood CML has been confirmed in multiple studies [5-7]. More recently, initial pediatric data is now available for second generation TKIs, including dasatinib and nilotinib [8,9]. TKI mono-therapy is considered standard therapy for those presenting in CP with adequate disease response. HSCT is now considered only in a subset of children with CML, namely those who present with, or progress to, blast phase. Potential side effects of TKIs that may be problematic in children include musculoskeletal events, growth restriction [10] and decreased bone mineral density [11]. Recent adult trials have demonstrated that some patients with stable CML with a sustained deep molecular response can safely stop TKI therapy without relapsing [12-14]. Data on the safety of ceasing TKI therapy in children with CML is extremely limited [15].

Permanent eradication of leukemia stem cells by HSCT could be argued as a reasonable approach to CML therapy [2], given the potential lifetime exposure to TKI therapy at critical growth periods in childhood, along with the with limited data on long-term side effects and the biologic differences between childhood and adult CML [2,16]. Information is limited regarding specific treatment choices, disease outcomes and morbidity of the two treatment strategies in children. Additionally, outcome data after pediatric patients with CML who fail first line TKI therapy, develop blast phase or are refractory to *any* TKI treatment, are limited.

This population cohort examines the outcomes of children with CML treated in the province of Ontario over a 30+ year period.

Methods

A multicenter retrospective analysis of patients with CML diagnosed between 1985 and 2018 was conducted across five pediatric oncology centers in the province of Ontario, Canada. Patients were identified through the Pediatric Oncology Group of Ontario Networked Information System (POGONIS). POGONIS is a population based cancer registry that collects demographic, disease and treatment details on all pediatric cancer cases diagnosed and/or treated at one of the five tertiary care centers in Ontario. Additional clinical details were abstracted from patient medical records to supplement the data available in POGONIS. Children and adolescents <18 years of age with confirmed BCR-ABL1 transcripts were included. Phase of disease at diagnosis and response assessment were classified as per the ELN guidelines [17]. Descriptive statistics were used to summarize patient and treatment characteristics, along with outcomes. Statistical analyses and Kaplan Meier curves were performed with GraphPad Prism software version 6.03 (GraphPad Software Inc.). Each participating institution provided IRB approval.

Results

With a population estimate of 14.7 million in the province of Ontario [18], from 1985 to 2018, 52 children and adolescents diagnosed with CML within the pediatric oncology system in Ontario were identified. Baseline patient characteristics are presented in table 1. Median age of patients was 10.5 years (1.8 -18 years). The majority of patients presented in the chronic phase (88%). The most common symptoms at presentation were bone pain and fatigue (each occurring in 28% of patients). Seventeen percent of patients were asymptomatic at diagnosis. Seventy-two percent of patients had splenomegaly on exam at diagnosis. Imatinib was first incorporated into treatment plans in 2002; this time point is used as a dividing factor to evaluate patients in the pre and post TKI era. From 1985 to 2002, twenty-two patients did not receive TKI therapy (figure 1). The majority of these patients (18/22, 82%) received treatment that included HSCT (matched sibling donor= 11, matched unrelated donor= 4, haploidentical donor = 2, autologous HSCT = 1). Four patients were unable to receive HSCT in the pre TKI era because no donor was available. Patients who underwent HSCT in the pre TKI era presented in CP (n = 14), AP (n = 1), BP (n = 3). Ten of these patients were reported as having achieved a complete hematologic remission prior to HSCT (56%). The overall survival for the entire pre-2002 cohort at a median follow up of 6 years was 63.6% (14/22). Of the eight patients who died, four died without having received a transplant (causes; blast crisis (n =2), refractory thrombocytopenia leading to massive intracranial hemorrhage (n = 1), one cause of death was unreported (n = 1). Four patients died post HSCT (causes; progressive disease post HSCT (n = 1), bronchiolitis obliterans organizing pneumonia (n =1), graft versus host disease and sepsis (n = 1), HSV pneumonia post HSCT (n= 1)).

The “TKI era” cohort consisted of thirty patients. Twenty-three patients were treated with

imatinib as first line therapy; four patients were treated with dasatinib as first line therapy. Fifty-two percent of patients that were started on imatinib remained on this TKI at last follow-up. Elective HSCT was performed upfront without the use of TKI therapy in three patients. TKIs were used exclusively as first line therapy in all institutions from 2005 onwards (see table 2). Of those that initially responded to TKI therapy, complete hematologic response was achieved at a median of 2 months (range 1-4 months). Complete cytogenetic response was achieved at a median of 7 months (range 1 – 17 months). Major molecular response was achieved at a median of 8 months (range 1-32 months).

Nine patients treated upfront with TKIs underwent HSCT from 2005-2018. Two of these patients underwent HSCT electively between 2002-2005, after TKI treatment was initiated. One patient had BC at diagnosis and underwent HSCT after one month of TKI therapy. Six of these patients underwent HSCT secondary to poor disease response to TKI therapy (three patients did not obtain a cytogenetic remission and three patients developed BC on TKI therapy). TKIs were continued post transplant in four patients for a varied period of time. Of the nine patients who underwent HSCT after TKI therapy, three patients died (all had matched unrelated HSCT). All three deaths were related to HSCT complications.

One patient who developed resistance to imatinib was switched to dasatinib and HSCT deferred secondary to family decision. This patient is still alive and in remission (this was the only patient for whom HSCT was not performed after initial TKI failure). The overall survival of all patients treated in the TKI era at a median follow up of three years was 90% (27/30). Survival of patients who remained on a TKI was significantly improved compared to those who underwent HSCT post TKI therapy (100% vs 66%, p = 0.008, figure 2). Comparing outcomes pre and post 2002, survival was similar between those who underwent HSCT after 2002 and *all* patients pre-2002 (figure 3). In contrast patients treated with TKI alone had

remarkably better outcomes (figure 3).

TKIs were well tolerated in this cohort. Two patients had side effects from imatinib (GI upset, joint effusions) and were switched to dasatinib with resolution of symptoms. WHO height centile changes from time of diagnosis until last follow up were recorded in patients ≤ 12 years to investigate if TKIs caused a change in height velocity in individual patients over time, compared to HSCT. The change in height velocities over time was averaged for each group; both groups had a slight decrease in height velocity from diagnosis (approximately 0.5 centile height decrease In both groups). This difference in height velocities between groups was not significant: HSCT (mean = 0.57 centile height decrease, SD = 0.38), TKI monotherapy (mean = 0.56 height centile decrease, SD = 0.29), $t(13) = 0.02$, $p = 0.98$.

Discussion

This report is based on a population of pediatric patients with CML treated in Canada. This population-based assessment enabled us to investigate the management of CML across five pediatric oncology centers, thus giving us a good sense of the real-world management of this disease, outside of a clinical trial. Our study supports the use of TKI mono-therapy in childhood CML, given the decreased mortality in those who received and responded to imatinib. Imatinib was well-tolerated and only discontinued in two patients secondary to refractory nausea and unexplained joint effusions. Additionally, there was no significant effect on growth parameters in patients using TKIs, compared to those who received HSCT.

Current recommendations suggest HSCT for children with progression to BP while on a TKI. For those who progress to AP while on TKI therapy, recent recommendations are to initiate

treatment with a second generation TKI; HSCT should be postponed as long as no failure to second line treatment is suspected [19]. Likewise, switching to a second generation TKI followed by monthly monitoring for 3 months is recommended for patients with imatinib failure, without an identified mutation [19]. Our data is in agreement with these recommendations, given the increased mortality associated with HSCT in this cohort. Patients who had a poor response to TKI therapy and had a HSCT had worse outcomes compared to those who received TKI mono-therapy. Although patients that underwent HSCT after TKI therapy were a more heterogeneous group in terms of disease status at time of HSCT (with some patients having more aggressive disease features than patients receiving TKI monotherapy), the three deaths in the HSCT group in the TKI era were all related to transplant complications. One patient who received dasatinib after imatinib failure (secondary to family preference) is alive and in remission. Given that no death was attributed to the primary disease process, the effectiveness of HSCT at eradicating CML is not debated. However the increased mortality associated with this treatment suggests further advances in HSCT may be required to outweigh the benefits of a TKI mono-therapy approach in the vast majority of childhood CML patients.

There are three key limitations of this study. First, our population cohort captured patients cared for in the pediatric system. It is likely that there were adolescent patients diagnosed in this period that were cared for in adult oncology programs and are not included in this analysis. For this reason, we are unable to report or comment on the incidence of childhood CML over time. Second, data captured did not include several potentially important elements including information on medication compliance, discontinuation of TKI therapy and laboratory data on mutation screening for TKI resistance. Third, each institution had a different method of managing medical data, with only two institutions maintaining electronic heath records; there were incidents when specific data was missing from paper charts and not available for extraction (symptoms at diagnosis were not reported/available in five

patients).

In conclusion, TKI therapy is a safe, effective treatment for childhood CML that has decreased mortality in children with this disease. In our cohort, no patient treated with a TKI died of progressive disease and all patients died related to HSCT complications. While HSCT is recommended for patients with particularly aggressive features, our results suggest further advancements in outcomes for children with CML will require either improvement in HSCT and/or optimization of medical therapy that overcomes the need for HSCT. For patients with primary refractory disease, or those who progress on TKI therapy, our data supports the current recommendations to switch to an alternative second generation TKI with HSCT delayed where possible. HSCT should be reserved for patients with blast phase disease, particularly those that evolve while on TKI therapy.

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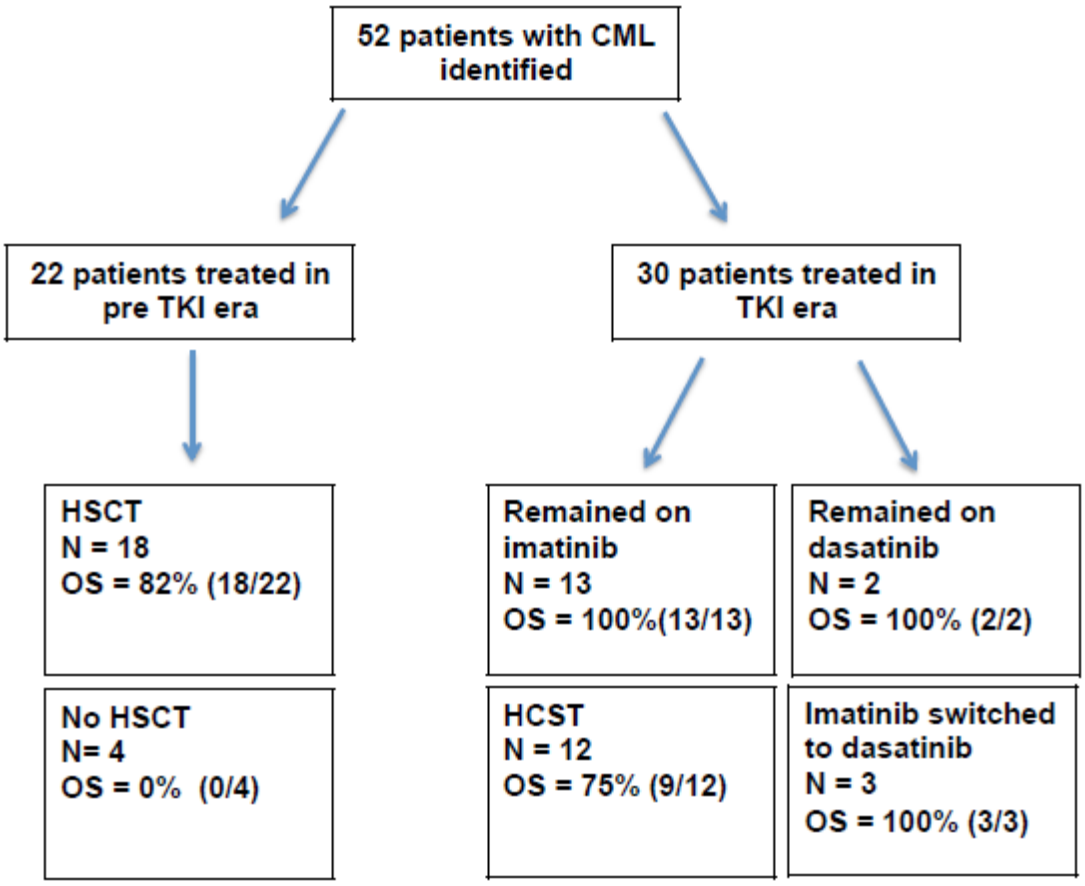

FIGURE 1. Flowchart identifying all pediatric patients with CML treated between 1985 and 2018.

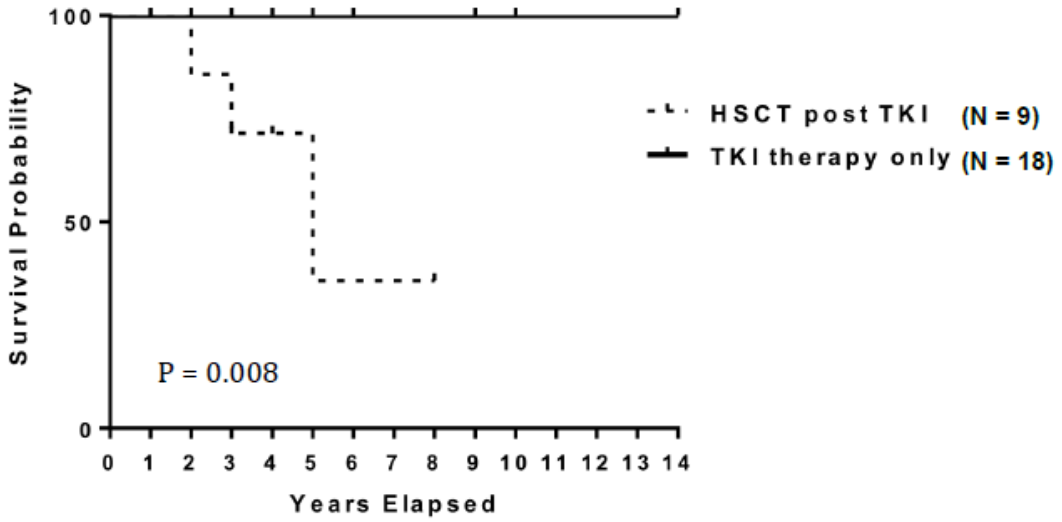

FIGURE 2. Survival of patients with CML who remained on TKI therapy versus those that underwent HSCT. Kaplan-Meier survival curve using the log-rank (Mantel-Cox) test demonstrated significantly improved survival in patients who received TKI therapy compared to those who underwent HSCT post TKI therapy.

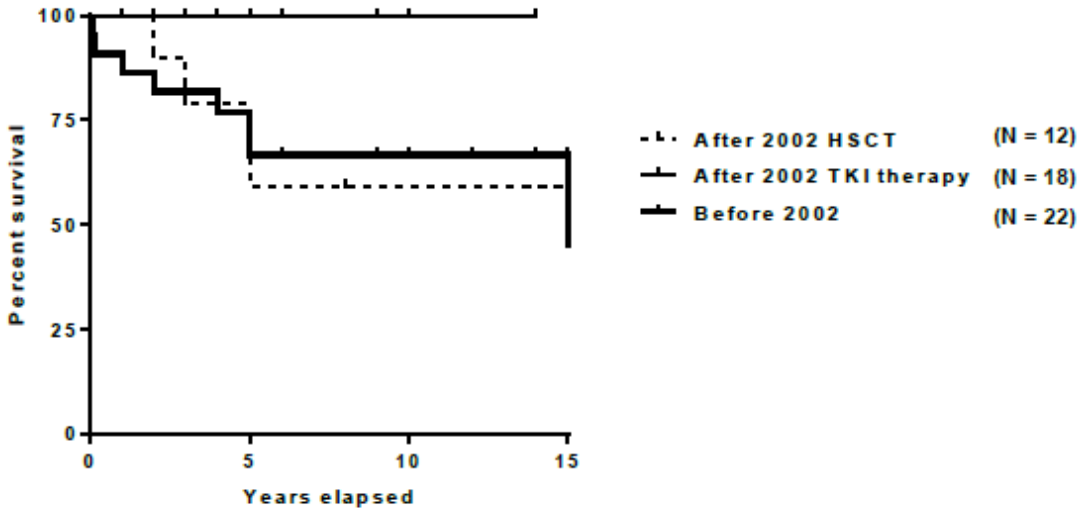

FIGURE 3. Survival of patients with CML before 2002 vs after 2002. The after 2002 cohort was divided into those who received TKI monotherapy and those who underwent HSCT (75% receiving TKI therapy before HSCT). The majority of the pre-2002 cohort underwent HSCT (82%).

TABLE 1

Clinical features of entire cohort at diagnosis (n = 52)	
Age at diagnosis (years), median (range)	10.5 (1.8-18)
Male: Female	29:23 (56%: 44%)
Symptoms at diagnosis* %:	
Bone pain	28%
Fatigue	28%
Abdominal pain	21%
Abdominal fullness	21%
Fever	17%
Weight loss	17%
Bruising	13%
Retinal hemorrhage	2%
Blurred vision	2%
Ankle swelling	2%
Priapism	2%
Skin lesion	2%
Asymptomatic	17%
Splenomegaly identified on exam	72%
WCC, median (range)	241 (25-683)
Hgb, median (range)	88 (37-170)
Platelets, median (range)	536 (13-2178)
Stage at diagnosis (%):	
Chronic phase	46 (88%)
Accelerated phase	1 (2%)
Blast phase	5 (10%)

***Data was available regarding symptoms at diagnosis in 47 patients**

TABLE 2

Characteristics of patients treated in the TKI era (n = 30)	
TKI used upfront:	
Imatinib	23
Dasatinib	4
No TKI used	3
Dose of Imatinib (mg/m2) median (range)	300 (260-340)
Reason for discontinuing initial TKI:	
Elective transplant in CP (2002-2005)	2
Poor disease response*	8
Intolerance (GI upset, joint effusion)	2
Received HSCT	12
Donor Source	
Matched sib donor	5
Matched unrelated donor	7
Overall survival (%)	
HSCT after TKI use	6/9 (66%)
HSCT with no TKI use	3/3 (100%)
Imatinib monotherapy first-line	13/13 (100%)
Dasatinib monotherapy first-line	2/2 (100%)
Switch from imatinib to dasatinib	3/3 (100%)

*** 3 patients developed blasts crisis, 3 patients failed to achieve cytogenetic remission, 1 patient developed resistance to TKI therapy, 1 patient presented with BC at diagnosis**