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Imatinib in the Treatment of Chronic Myeloid Leukemia in Children and Adolescents is Effective and well-tolerated. Report of the Polish Pediatric Study Group for Treatment of Leukemias and Lymphomas

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Abstract

Chronic Myeloid Leukemia (CML) constitutes only 2-3% of all leukemias in pediatric patients. Philapelphia chromosome and BCR-ABL fusion are genetic hallmarks of CML, and their presence is crucial for targeted molecular therapy with Tyrosine Kinase Inhibitors (TKI), which replaced Hematopoietic Stem Cell Transplantation (HSCT) as a standard first-line therapy. The disease in pediatric population is rare, and despite molecular and clinical similarities different approach is warranted due to long lifetime expectancy and distinct developmental characteristics of affected children. We have analyzed the results of treatment with imatinib in 57 pediatric patients from 14 Polish Pediatric Hematology Oncology Centres. In the study group 40 patients (pts) continue imatinib (median follow-up 23.4 months) while in 17 the treatment was terminated (median follow-up 15.1 months) due to therapy failure. In the latter group, 13 pts underwent HSCT while 4 switched to second-generation TKIs. 5-year Overall Survival (OS) in the study group was 96% and 5-year Event-Free Survival (EFS) 81%.

Keywords: Chronic myeloid leukaemia; Children; Adolescents; Imatinib

Introduction

Chronic Myeloid Leukemia (CML) is a myeloproliferative neoplasm typically diagnosed in adult population and relatively rare in children with incidence of 0.6-1.2/ million per year [1]. CML is a clonal disorder of hematopoietic progenitor cells resulting from the balanced translocation (9:22) called Philadelphia chromosome (Ph) at molecular level resulting in formation of a fusion gene *BCR-ABL*. The *BCR-ABL* protein encoded by the fusion gene has an activity of tyrosine kinase and promotes uncontrolled proliferation of pluripotent stem cells in Bone Marrow (BM). CML has a three-phase course: Chronic phase (CML-CP), accelerated phase (CML-AP) and blast crisis phase (CML-BC). CML is most commonly diagnosed in the CML-CP and only in about 10% of cases in advanced phases: CML-AP or CML-BC [2].

Before the implementation of imatinib, hydroxyurea +/- interferon alpha remained the first line treatment of CML, followed by HSCT after achievement of hematologic remission [3]. The identification of Tyrosine Kinase Inhibitors (TKI) with BCR-ABL blocking ability revolutionized the CML therapy due to pharmacological control of leukemic clone. TKI-based therapy has proved to be very effective and quickly led to withdrawal of HSCT as the first-line treatment. A first generation TKI-imatinib was approved for treatment of adult patients in 2001. Then in 2003 it was approved for therapy in children. It should be emphasized that treatment with TKI is not a way to cure CML, as in most patients leukemia cells are still present. However, a unique feature of these drugs is a significant reduction of the risk of CML progression [2]. In the era of TKI, a CML-CP can last up and beyond 20 years.

The recommended starting dose of imatinib for children is 260-300 mg/m^2 (maximum daily dose 400 mg) in CP, 400 mg/m^2 (maximum daily dose 600 mg) in AP and 500 mg/m^2 (maximum daily dose 800 mg) in blastic phase [3]. In recent years due to the development of the targeted therapy and implementation of TKI in pediatric patients too, there has been a significant progress in the treatment of CML but the data is relatively limited due to low incidence of CML. One should remember that long-term side effects of TKI therapy may occur, because the drug has only been in use for approximately 15 years. Despite the excellent results of imatinib therapy one should not forget about HSCT. It is the only method for obtaining definite cure of CML. HSCT is the first line treatment in patients with CML, who have become resistant to the first and second generation TKI or when serious side effects of the therapy occur and there is a matched donor available. In some cases, the preference of HSCT by the patient or his/her parents is also very important. It is worth noting that HSCT should be considered more frequently in patients diagnosed with CML before puberty due to growth impairment after TKI. The transplant is in fact the only method that allows cure for this disease.

Aim of the Study

Evaluation of treatment with imatinib in Polish pediatric patients with CML.

Materials and Methods

We conducted a retrospective, nation-wide analysis of the imatinib therapy results in children and adolescents with CML in Poland. The study group consisted of 57 patients (M=35, F=22) from 14 Polish Pediatric Hematology Centers treated in years 2006-2016. Majority of patients (n=54) were diagnosed in chronic phase and only three patients in accelerated phase. The diagnosis of CML was made according to 4th edition of WHO classification of hematopoietic and lymphoid tissues, with mandatory molecular confirmation of BCR-ABL1 fusion. The first line treatment with imatinib was performed accordingly to I-BFM recommendations. Patients and/or their legal guardians have signed appropriate consents.

The effectiveness of TKI therapy was evaluated on the basis of "milestones" of the therapy: Complete Hematologic Remission (CHR), Complete Cytogenetic Response (CCyR) and Major Molecular Response (MMR). CHR was defined as leukocyte count<10 × 103/μL, <5% basophils and <450 × 103/μL platelets in peripheral blood, absence of myelocytes, promyelocytes and blasts in the peripheral blood and non-palpable spleen during physical examination. Starting from the moment of CML diagnosis blood counts with blood smear should be performed every 15 days until achieving CHR and then at least once every 3 months. Complete cytogenetic response was defined as the absence of Ph (+) Cells in Bone Marrow (CyCR) in classical cytogenetics or FISH method and evaluated within 12 months of the treatment.

Partial Cytogenetic Response (PCyR) was the presence of from 1% to 35% Ph (+) cells in the bone marrow. Minor and minimal cytogenetic response was the presence of from 36% to 65% or from 66% to 95% Ph (+) cells in the bone marrow, respectively. Cytogenetic evaluation was performed after 3 and 6 months from the implementation of imatinib, then every 6 months till CCyR achievement and every 12 months thereafter or in case of treatment failure.

Molecular response was evaluated after 18 months of the treatment. Major molecular Response (MMR) was defined as the of BCR -ABL transcript level below 0.1% Molecular tests were performed every 3 months until MMR confirmation and then not less than every 6 months. If there was an unsatisfactory response testing for BCR-ABL kinase domain mutations was performed.

Statsitical analysis

The statistical analysis was performed using STATISTICA 10.0. As events in the analysis of Event-Free Survival (EFS) we considered: death of the patient, switch to second generation Tyrosine Kinase Inhibitors (2GTKI) due to therapy failure or imatinib intolerance, proceeding with HSCT due to intolerance of imatinib and or loss of cytogenetic or molecular response during imatinib therapy.

Results

Study group. The median age at CML diagnosis was 13.6 years (the youngest child was 1.2 year, the oldest 17.9 years). The most commonly reported symptoms at the diagnosis were: asthenia (n=22), weight loss (n=18), abdominal pain (n=17), fever (n=16), limb pain (n=10), and hemorrhage (n=7). Other reported symptoms included: ecchymosis (n=4), headache (n=4), diplopia (n=2), pallor (n=2), cough (n=2), priapism (n=2), breast pain (n=1), night sweats (n=1), arthritis (n=1), dyspnea (n=1), polydipsia (n=1), hair loss (n=1) and intramuscular hematoma (n=1). The most frequent signs were splenomegaly (n=43, median size of the spleen was 5.5 cm below the costal margin) and hepatomegaly (n=34, median size of the liver was 3 cm below the costal margin). In eight cases the diagnosis was set on the basis of routine blood test without other accompanying symptoms. Laboratory tests revealed significant hyperleukocytosis in majority of patients-median 226.28 103/μL (range 7.17 - 810 103/μL) and thrombocytosis-median 471 103/μL (range 27.9 - 3444.7 103/μL). During follow-up period two patients died, both after transplantation. One of them died on day +307 after HSCT of central nervous system aspergillosis and multiorgan failure, while the second one on day +76 after HSCT of grade IV acute Graft versus Host Disease (aGvHD) and pulmonary hemorrhage. 5-year OS in the study group was 96% in **Figure 1** and 5-year EFS was 79% in **Figure 2**.

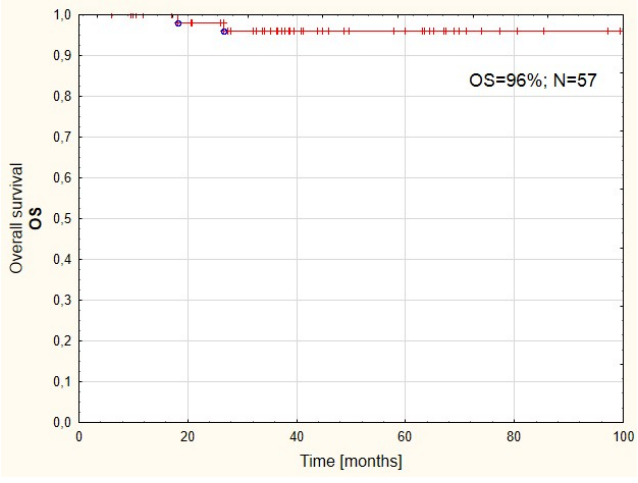

Figure 1: Overall survival.

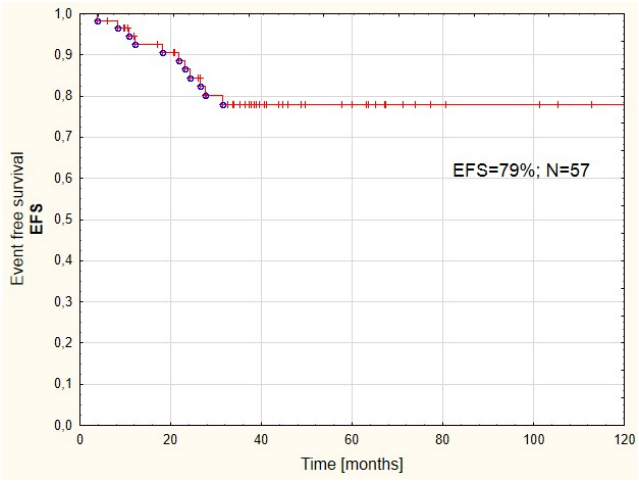

Figure 2: Event free survival.

Treatment with imatinib

All pediatric patients were qualified for first-line treatment with imatinib, according to CML-PAED II and I-BFM-CML protocol. Hydroxyurea was administered as pre-imatinib cytoreductive phase in 21 patients (median duration: 16 days). In one case anagrelide was administered alternatively for the treatment of CML-associated thrombocytosis. The median time of imatinib implementation from the moment of diagnosis was 7 days (range 0-202 days). The median initial dose was 300 mg/m^2 (range 220 mg/m^2 to 468 mg/m^2). The maximum dose was implemented in a single patient in CP, who has become resistant to the standard doses and experienced lack of CCyR and MMR in 12 and 18 months after initiation of therapy, respectively. The dose of imatinib during therapy was modified in 23 cases. In 13 patients the dose had to be increased from 300 to 400 mg/m^2 due to resistance to imatinib therapy. In 10 patients imatinib dose was reduced due to toxicity (n=8) or satisfactory response to higher dose (n=2) (median dose after reduction 170 mg / m2). Toxicity included: myelotoxicity (WHO grade 4, n=1), thrombocytopenia (n=1), leukopenia (n=5) and headache (n=1). In 4 patients 2GTKI were implemented after imatinib: dasatinib in 3 cases and nilotinib in 1 case. In 19 patients due to unsatisfactory response to imatinib testing for BCR-ABL kinase domain mutations was performed. In 3 cases the T315I mutation was confirmed and all these patients underwent HSCT afterwards. In one case ponatinib was and achieved molecaular remission.

Complete Hematologic Remission (CHR) within 3 months was achieved in 57 patients. In 2 patients we observed hematologic relapse. One patient underwent HSCT afterwards and the other was switched to 2G TKI-nilotinib and achieved second CHR.

Complete Cytogenetic Response (CCyR) within 12 months was evaluable in 45 out of 57 patients. In 4 cases follow-up period did not exceed 1 year, 4 patients underwent HSCT in less than 12 months from the start of treatment, 2 patients were transferred to an adult ward before evaluation while in 2 patients cytogenetic response was not assessed. CCyR within 12 months from the onset of therapy was achieved in 31/45 patients (i.e. 69%). CCyR after 12 months was observed in 9/45 cases (i.e. 20%). CCyR was not achieved in 5 cases (i.e. 11%). Of 5 who failed to achieve CCyR 3 patients were switched to dasatinib and 2 patients underwent HSCT afterwards.

Major Molecular Response (MMR) after 18 months was evaluable in 46 out of 57 patients. In 5 cases the follow-up period did not reach 1.5 year 0.4 patients underwent HSCT in less than 18 months from the start of treatment and 2 patients were transferred to an adult ward. MMR was achieved in 28/46 patients (i.e 61%) after 18 months from the beginning of treatment. MMR later than 18 months from therapy start was seen in 8/46 patients (i.e 17%) with median time of 24 months. MMR was not achieved in 10/46 cases (i.e 22%). Five of these patients underwent HSCT afterwards and 2 were switched to 2G TKI-dasatinib. In 3 cases the dose of imatinib was increased, with continuous decrease in BCR-ABL level. Characteristics of the study group and the results of treatment are summarized in **Table 1**.

	Number of patients
Patients total	57
Male	35
Female	22
Phase at the diagnosis	
Chronic phase	54
Accelerated phase	3
Hematologic remission	
Complete hematologic remission (CHR)	55
Hematologic relapse	2
Cytogenetic response evaluable	45/57
CCyR within 12 months	31 (69%)
CCyR after 12 months	9 (20%)
Failed to achieve CCyR	5 (11%)
Switch to dasatinib	2
HSCT	3
Molecular response evaluable	46/57
MMR within 18 months	28 (61%)
MMR after 18 months	8 (17%)
Failed to achieve	10 (22%)
HSCT	5
Switch to dasatinib	2
Increase of the imatinib dose	3

Table 1: Characteristics of the study group.

Hematopoietic Stem Cell Transplantation (HSCT) was performed in 13 children (M=9, F=4). In 4 patients the transplant was performed in the first CML-CP due to the local preference of the center. In 3 patients the reason for HSCT was advanced phase of CML (CML-BC, n=1; CML-AP, n=2) and these children were transplanted in the second CP

(CML-CPII), after TKI treatment. Hematologic toxicity of imatinib was the reason for transplant in one case. In 5 other cases loss of molecular and/or cytogenetic response were observed. The donors were either matched unrelated (MUD: n=9) or sibling (MSD: n=4). Median time from the diagnosis of CML to HSCT was 14.8 months (range 5.7 months-49 months). In 9 children HSCT was performed in first CP and in 3 cases in the second CP. In one case reduced-intensity conditioning regimen according to CML-SCT I-BFM study was introduced. So far tests confirm 100% allogenic chimerism and non-detectable BCR-ABL (MR 4.5) in patient's peripheral blood but the follow-up period is too short (2 months) to confirm the complete success of transplantation.

Out of 57 patients enrolled in the treatment 40 patients continue therapy with imatinib, while 17 completed the treatment. 35 patients continue the therapy in pediatric centers (median follow-up 33 months) and 3 patients in adult centers with which we are in constant contact (median follow-up 93 months), while 2 patients were lost to follow-up after being transferred to adult centers (status at the last contact: continuation of the TKI therapy). Among patients who completed the treatment 13 underwent HSCT (2 patients died due to complications of the post-transplant period) and 4 patients were switched to second generation TKI (dasatinib, n=3; nilotinib, n=1).

Discussion

Clinical data concerning the treatment of CML in pediatric population are limited because of its low incidence in children. It should be noted that for the purpose of our analysis we have gathered a relatively large group of patients (n=57) when comparing with the available literature. The entire observation period amounted for 33 months in patients who continue the treatment in pediatric centers and 93 months in patients who continue the treatment in adult centers.

Hematopoietic stem cell transplantation

Before the era of imatinib HSCT was a standard first-line therapy Among pediatric patients who underwent transplantation from MSD in the first chronic phase (CML-CP) in the years 1982 to 2004 EFS during the observation period of 3 to 5 years after HSCT ranged from 61% to 63%. OS ranged from 66% to 87% [4,5]. In patients transplanted from MUD results were inferior with EFS ranging from 27% to 55% and OS from 45% to 65% [4-7]. The main cause of death in both groups was acute and chronic GVHD more common in children after MUD-HSCT. In patients transplanted in advanced phase (CML-AP or CML-BC) or the second chronic phase (CML-CPII), the results were worse with EFS from 34% to 35% and OS from 39% to 46% [6]. In our study group only 13 patients underwent HSCT, which was mainly due to the good response to TKI therapy in most cases. OS among these children was 86%. We should remember that despite giving up the use of HSCT as a first-line therapy it is still the only method by which we can completely eliminate leukemia cells and cure the disease.

Treatment with imatinib

One of the first trials with TKI in children was published in 2004 by the Children's Oncology Group with promising results [8]. For the second phase trial of this study 31 pediatric patients were qualified who experienced failure of interferon therapy. In this group all children achieved CHR and in 83% of them CCyR was observed. Another study covered 8 European countries and 30 patients were enrolled in it [9]. CHR was achieved in 80% cases and CCyR in 60% of the patients enrolled in the trial in the CP and 29% of children enrolled in AP. In half of the children MMR was reported. Similar results were published in France in the fourth phase study conducted on a group of 40 patients [10]. The average duration of follow-up period in this study was 16 months. CHR within 3 months was achieved in 86% of the patients and within 6 months in 98% of the patients. CCyR was observed in 62% of the children within one year after the inclusion of imatinib therapy, in 34% of them MMR within 18 months after initiation of the treatment was confirmed. Similar results were achieved in a German clinical trial CML-PAED II published in year 2009 [11]. Out of 42 enrolled patients 40 achieved CHR within 3 months. In 26 out of 28 patients CCyR was observed within one year after the start of the treatment and in 17 out of 19 MMR after 18 months from the onset of treatment. It should be emphasized that all patients from our study group are simultaneously registered in an international database I-CML-Ped Study, consisting so far of 351 children diagnosed with CML. This study aimed at optimizing the treatment of CML in children is ongoing. Preliminary results presented at the 56th ASH Annual Meeting are promising and comparable with the results of treatment achieved in Polish population [12]. Our study group consisted of 57 pediatric patients diagnosed in Poland with a median overall follow-up period of 31 months. CHR within 3 months after implementation of the treatment with imatinib was documented in all patients. CCyR after 12 months of therapy was observed in 69% of patients while MMR in 61% of patients after 18 months of treatment. These results correspond with the quoted literature in particular with the results of Suttorp et al. analysis from year 2009 and the results of treatment in the context of clinical trial CML- I-Ped Study [11,12]. Moreover, when comparing the proportion of patients achieving CCyR and MMR our results are above promising. Although, despite the excellent results of imatinib therapy one should not forget about HSCT. It is worth noting that HSCT should be considered more frequently in patients diagnosed with CML before puberty. Due to the fact that long-term TKI intake may be the cause of short stature in the future among these patients [13].

Side effects of imatinib

TKI are usually well tolerated however some side effects may occur. In most cases they are classified as mild to moderate and occur mainly in patients in whom TKI therapy was introduced in advanced phases of CML. Non-hematological, relatively common side effects include: nausea, vomiting, diarrhea, skin rash, swelling, limb pain, muscle spasms, bone and joint pain, headaches, weight gain and an increase in liver enzymes [4,9,10,14]. In one of our patients we documented severe headache, which resolved after a temporary decrease in the dose of imatinib. Millot et al. described neutropenia grade 3 or 4 in 27% of children receiving imatinib, thrombocytopenia grade 3 or 4 in 5% and anemia grade 3 or 4 in 2.5% of the patients [15]. However, these cytopenias were treatable by the temporary discontinuation of the therapy or administration of G-CSF in some children with neutropenia. In 5 of our patients we observed leukopenia and in 1 thrombocytopenia which also resolved after a temporary dose reduction of imatinib. Only in 1 case myelosuppression as a side effect after imatinib implementation was a reason for HSCT. Despite the potential cardiotoxicity, hepatotoxicity, immune disorders and thyroid gland dysfunction observed in adults treated with imatinib, in children they have not been documented so far [16]. In the group of pediatric patients with CML the aspect of TKI therapy impact on bone metabolism is very important. Imatinib impairs differentiation and

reduces the activity of osteoblasts and osteoclasts. This can result in growth retardation in children, particularly those who are starting the treatment in prepubertal age [13,17,18,]. In our study group we observed no impact of imatinib on calcium and phosphate metabolism. We also noticed no abnormalities in serum phosphate, calcium, Parathyroid Hormone (PTH) and vitamin D level or tubular function disorders (phosphate absorption). However, we should keep in mind that particular attention should be paid in the group of the youngest patients chronically receiving TKI. They require regular and detailed clinical evaluation and performing the panel of basic laboratory tests during each visit. Our results confirmed that the recommended daily dose of imatinib is well tolerated in pediatric patients and severe side effects are relatively rare.

Second generation TKI

2G TKI - dasatinib and nilotinib were registered for the treatment of adult patients with CML in 2006 and dasatinib only for the therapy in children in 2007. Nilotinib is not currently recommended for the treatment of pediatric patients. 2G TKI are recommended when intolerance or resistance to imatinib occur [19,20]. They are more effective in the treatment of CML due to the linking both active and inactive conformations of the BCR-ABL protein. In addition, they show greater activity in the case of mutations of BCR-ABL gene associated with resistance to TKI therapy [21]. Unfortunately, there are an even more limited number of studies on the use of 2G TKI in children. The first reports are from 2011 as the results of the first phase clinical trial conducted by the Children's Oncology Group. 39 patients were enrolled for the treatment with dasatinib, including 9 with CML who were resistant to imatinib or who had an adverse event after using it. In 8 patients cytogenetic response was observed, in 3 CCyR, in 3 PCyR, in 1 minor and in 1 minimal cytogenetic response. In 1 patient the cytogenetic response was not possible to assess [22]. The first phase study CA 180-018 from year 2013 was conducted on a group of 63 pediatric patients, 17 of which were enrolled in chronic phase of CML and only 3 in advanced phase. Among patients with CML-CP CHR was achieved in 94%, CCyR in 82% and MMR in 47%. Patients enrolled in the study in advanced phase of CML achieved slightly worse results [23]. In our study group dasatinib was administered in 3 patients while nilotinib in one case. In all 4 cases these drugs were implemented due to the failure of imatinib treatment. Patients continue the treatment with 2G TKI with satisfactory outcome and no side effects were documented. Clinical trials on the use of 2G TKI are being carried out and are raising great hopes, especially in patients in whom imatinib has proven to be ineffective.

Discontinuation of the treatment

Observations in adult patients show that during the TKI therapy and after documentation of undetectable level of BCR- ABL over a period of 24 months or more one can try to discontinue the treatment with imatinib [24-26]. Approximately in 40% of these patients one can confirm continuous MMR despite cessation of the therapy. In our study group, treatment was discontinued in one patient after continuous 26 months of undetectable level of BCR-ABL. The patient remained under a constant control and after 11 months of continuous MMR molecular relapse was confirmed (level of BCR-ABL transcript 3%). Imatinib was reintroduced and patient achieved second MMR within 3 months. The results of controlled trials evaluating the efficacy of TKI withdrawal in the groups of pediatric patients are promising but they have not been published yet [26]. These results will be very important because of the potential side effects of long-term therapy with imatinib.

Conclusion

Our results confirm that introduction of TKI therapy has revolutionized the treatment of CML in the pediatric population by replacing previous method of treatment with HSCT and allowing a high percentage of OS (96%) and EFS (81%). Although the use of TKI and 2G TKI is not a cure for CML and only reduces the risk of disease progression significantly, the results of ongoing clinical trial evaluating the safety of the treatment withdrawal after confirming a continuous 24-month undetectable level of BCR-ABL are promising. Despite the initial enthusiasm due to the excellent results of TKI therapy there are more reports confirming that the use of imatinib is not devoid of serious side effects. Although in our study group in only one case we observed myelotoxicity WHO grade 4, which was the reason for HSCT afterwards. We should keep in mind the fact that the goal of the therapy in pediatric patients should be rather to cure the disease than the disease suppression, which can be achieved only by performing HSCT. In the context of very promising results of HSCT in pediatric patients with CML after reduced-intensity conditioning regimen (S. Matthes-Martin, personal communication) HSCT should be considered especially in prepubertal children.

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