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REVIEW

Profile of imatinib in pediatric leukemia

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Abstract: Using targeted therapy for treatment of cancer has become the paradigm to which clinical trials aspire. Imatinib, the *BCR-ABL1* tyrosine kinase inhibitor (TKI), was the first of its kind to specifically target and inhibit the underlying Philadelphia chromosome (Ph+) onco-gene found to be driving chronic myeloid leukemia in adults, and has since become standard of care for the treatment of chronic myeloid leukemia in children. Imatinib, with its ability to target Ph+ leukemia, has been successfully incorporated into the treatment of not only pediatric chronic myeloid leukemia but also Ph+ acute lymphoblastic leukemia. With the incorporation of imatinib into combination chemotherapy for pediatric Ph+ acute lymphoblastic leukemia, current survival rates are far higher than at any other time for this once dreadful disease. With more children today receiving treatment with imatinib for either chronic myeloid leukemia or Ph+ acute lymphoblastic leukemia, knowledge is accumulating surrounding the short-term and long-term toxicities observed in children, adolescents, and young adults treated with this TKI. In summary, the TKI imatinib has made a historic impact in the treatment of pediatric Ph+ leukemias, transforming what were once very high-risk diseases with considerable morbidity and mortality into ones that are now very treatable but with a new awareness surrounding the long-term toxicities that may come with this price for cure.

Keywords: imatinib, leukemia, lymphoblastic leukemia, chronic myeloid leukemia, pediatric

Introduction

Imatinib (Gleevec®, Novartis, Basel, Switzerland) is a rationally designed drug designed to selectively inhibit the tyrosine kinase domain in the Abelson proto-oncogene (*ABL1*) found to be constitutively active in both chronic myeloid leukemia (CML) and Phila-delphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL). Imatinib not only inhibits the *BCR-ABL1* of CML and Ph+ of ALL, but targets the tyrosine kinases c-kit and platelet-derived growth factor receptor, both of which are driving mutations found in myeloid and lymphoid malignancies.[1,2] Imatinib was initially approved by the US Food and Drug Administration for the treatment of CML in May 2001 and was most recently approved on January 25, 2013 for the treatment of children with newly diagnosed Ph+ ALL.

Based on the successful experience incorporating imatinib into treatment of adults with Ph+ leukemia,[3–6] imatinib has been tested in pediatrics and since become a stan-dard approach for children with either CML or Ph+ ALL.[7,8] This review summarizes the clinical experience using imatinib in pediatric CML and Ph+ ALL, and provides an overview of what is currently known regarding long-term toxicities with imatinib,

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particularly those pertaining to children that may be more unique than those seen with their adult counterparts.

Imatinib for pediatric CML

CML is a relatively rare leukemia in children, adolescents, and young adults (aged 15–39 years), comprising 2%–3% of all childhood leukemia, with an estimated 170 cases diagnosed under the age of 20 years in North America in 2013.[9] CML is a clonal disorder involving hematopoietic stem cells that harbor the Ph+. The Ph+ is the result of a reciprocal translocation involving a region of the long arms of chromosome 9 and chromosome 22, t(9;22)(q34;q11),[10] which results in a novel fusion gene *BCR-ABL1*, encoding a constitutively active tyrosine kinase.[11] Imatinib is a selective competitive inhibitor of the *BCR-ABL1* tyrosine kinase fusion gene identified in CML. Prior to imatinib, the primary treatment for children diagnosed with CML was myeloablative hematopoietic cell transplantation (HCT) using either related or unrelated donors.[12–15] Although HCT offered curative therapy to children with this disease, transplant-related mortality and development of graft-versus-host-disease were significant barriers to this treatment approach.[12,13]

Based on the impressive activity observed in adults with CML using imatinib,[3] the Children's Oncology Group investigated this novel tyrosine kinase inhibitor (TKI) (at dose levels of 260–570 mg/m^2) in a Phase I study for children with Ph+ leukemia.[16] Fourteen of the 31 patients enrolled had a diagnosis of CML. There was a single dose-limiting toxicity (grade 2 weight gain) occurring at the initial dose level, with no further dose-limiting toxicities observed during course 1, so no maximum tolerated dose was identified. The 2-year probability of a complete hematologic response (reduction of white cell count to <10,000 per μL and platelets <450,000 per μL maintained for 4 weeks) was 92%, with 83% (10/12) of the CML patients achieving a complete cytogenetic response (no evidence of Ph+ cells by fluorescent in situ hybridization) at a median of 3 months into therapy. The 2-year overall survival was 93%, with the one death being the result of complications following HCT.

The success of this Phase I study led to an open-label, multicenter Phase II study of imatinib (340 mg/m^2/day) given continuously to children with chronic phase CML (NCT00030394).[17] Fifty-five children were enrolled into this study between 2002 and 2004. The median age was 11.8 (2.3–19.1) years. Fifty-one children were evaluable for response with a median follow-up of 3.8 years. A complete hematologic response was observed in 9/48 (19%) patients after course 1 (28-day course) and 39/49 (80%) after course 2.

A complete cytogenetic response was observed in 33/46 (72%) evaluable patients at a median of 5.6 months' therapy, with 6/22 (27%) patients achieving a complete molecular response (undetectable *BCR-ABL1* by quantitative polymerase reaction). Imatinib was well tolerated, with the most common grade 3/4 adverse events consisting of anemia (14%), neutropenia (32%), thrombocytopenia (16%), myalgia (12%), elevated liver enzymes (6%), headache (2%), vomiting (2%), weight gain/edema (4%), and diarrhea (2%). Thirteen of the 51 patients (25%) developed recurrent disease after achieving a complete cytogenetic response and completing a median of eleven courses of imatinib (range 1–35). The majority of these relapsed patients proceeded to HCT, as did the remaining patients in this study who did not show evidence of disease recurrence. Overall, the progression-free survival and overall survival at 3-years was 72%±6.4% and 92%±3.9%, respectively.

Responses to imatinib in children with CML appear to be greater than what has been reported in adults in terms of response time. In the CML-PAED II study of 51 pediatric CML patients,[18] 95% achieved a complete hematologic response at 3 months, 93% achieved a complete cytogenetic response at 12 months, and 85% of patients achieved a major molecular response at 18 months, all much higher rates of response compared with prior adult studies.[3,19,20] Further follow-up in the CML-PAED II study, as of November 2012, reports 130 patients enrolled (mean age 10.8 years, range 1–17 years) with 80% (n=104) of patients still on imatinib.[21] Of the patients with chronic phase CML, 17% (21/126) experienced treatment failure on imatinib, that resulted in 17 patients switching to dasatinib, a second-generation TKI, and four receiving HCT. Based on the published success of adults with CML treated with imatinib alone, where the 6-year overall survival is 95% when only CML-related deaths are considered,[4] treating CML in children, adolescents, and young adults with imatinib has become more prevalent.[22,23] The decision to use imatinib alone in pediatric CML over HCT, which previously had been considered the gold standard for this disease, can be easier when a poorly matched donor or no donor is identified or in areas where HCT is not readily available.[24] In cases where an available matched sibling donor exists, pursuing HCT over imatinib remains controversial in pediatrics.[7,25,26] In a retrospective cross-sectional study of 33 pediatric patients with CML treated between 1994 and 2009, patients who had available HLA-matched related donors received HCT (n=14) while those without a donor received imatinib alone (n=19).[27] The 2-year disease-free

survival and overall survival data were not statistically different between treatment groups, reporting 59% and 82% disease-free survival (P=0.880) and 84% and 87% overall survival (P=0.714) for HCT recipients versus those treated with imatinib. Given the absence of a survival advantage with HCT in this series and the known risk of transplant-related mortality and graft-versus-host-disease that exists for HCT recipients, treatment for children with CML would seem to favor imatinib therapy alone. As improvements in transplantation continue to lower the morbidity and mortality that can be associated with the procedure (eg, transplant-related mortality and graft-versus-host-disease) in children with hematologic malignancies,[28] the optimal management of children with CML, ie, HCT versus medical therapy alone, should be readdressed.

In summary, despite the encouraging results to date for children treated with imatinib for CML, the idea of remaining on a TKI lifelong can be daunting. Recent reports of adults with chronic phase CML, who achieve a complete molecular response (undetectable *BCR-ABL1*) and maintain this for at least 2 years, show that around 40% can successfully discontinue imatinib without disease recurrence.[29–33] Whether the same or greater success can be achieved in children with CML who achieve a complete molecular response has yet to be determined and prospective clinical trials testing this hypothesis are awaited.[34]

With the premise that imatinib therapy for children, adolescents, and young adults with CML is lifelong, the burden of cost for the treatment of this disease can be daunting, particularly when compared with the "one-time" cost of HCT. In a cost analysis study performed in Mexico of 72 adult patients with chronic phase CML where 22 (31%) received reduced-intensity conditioning HCT and 50 (69%) were treated with imatinib alone, there was no significant difference in 6-year overall survival or failure-free progression.[35] What was striking was that the median cost of each reduced-intensity conditioning HCT ($18,000 US dollars) equated to a mere 180 days of imatinib treatment at 400 mg/day. Based on this analysis and others,[36,37] cost considerations often favor HCT over lifelong imatinib for patients with CML and may be part of the decision process as to whether to proceed with HCT or continue TKI therapy in patients with CML.

Imatinib for pediatric Ph+ ALL

Ph+ ALL comprises 3%–5% of ALL observed in children compared with 20%–30% in adults.[38,39] For years, this disease had been a near death sentence for children diagnosed and treated with chemotherapy alone, with reported

event-free survival rates of <30%.[40] HCT has been the preferred treatment for children with this very high-risk leukemia and improved survival to 40%–55% during the pre-imatinib era.[41–44] Based on the incredible success using imatinib for treatment of adults with CML, imatinib was soon incorporated into induction regimens for adults with Ph+ ALL. With the addition of imatinib, remission induction rates and overall survival were greatly improved in adults with Ph+ ALL compared with historical controls prior to the imatinib era.[5,6,45,46]

Based on the adult experience of safely incorporating imatinib into multiagent chemotherapy for Ph+ ALL along with the very poor outcomes observed in children with this disease, the Children's Oncology Group investigated imatinib added to an intensive chemotherapy backbone in an upfront study in children with Ph+ ALL.[8] Ninety-three patients with Ph+ ALL were enrolled. There were five cohorts investigating different treatment schedules, with cohort 5 testing continuous imatinib (340 mg/m^{2}/day). The toxicity profile of imatinib plus chemotherapy was similar to that in patients treated with chemotherapy alone, as this study also included very high-risk non-Ph+ patients. Toxicities that were significantly greater in the imatinib-treated patients included infection, with grade 3/4 neutropenia during the reinduction phase of the study. Imatinib-treated patients reported infection with grade 3/4 neutropenia at a rate of 19.6% compared with 2.2% for patients who did not receive imatinib (P=0.01). In addition, hypokalemia (P=0.04) and leukopenia (P=0.02) were more frequent in the imatinib cohorts. The patients enrolled into cohort 5, ie, receiving continuous imatinib, including those who went on to receive matched sibling HCT, had the greatest 3-year event-free survival (80.5%±11.2%), which was significantly greater than that for historical controls (<40%, P<0.0001).[47,48] There was no significant difference in event-free survival when comparing patients in cohort 5 who received imatinib and chemotherapy alone with those who underwent HCT with matched sibling donors or matched unrelated donors. Patients receiving imatinib and chemotherapy only (n=25) reported a 3-year event-free survival of 87.7%±10.9% compared with 56.6%±21.5% for matched sibling donor recipients (n=21) and 71.6%±19.0% for matched unrelated donor recipients (n=11, P=0.14). The study results were recently updated for cohort 5, with a minimum 6-year follow-up, and reported a 4-year event-free survival rate of 75%±9% for the imatinib/chemotherapy only patients compared with 64%±11% for matched sibling donor HCT and 64%±16% for matched unrelated donor HCT (P=0.77, unpublished data). These results are very encouraging as the

disease-free survival appears to be stable despite patients being off imatinib therapy for close to 2 years.

Despite the improved outcomes for children with Ph+ ALL treated with imatinib and chemotherapy alone, HCT continues to be used for some children with this disease, with imatinib incorporated into either the pre-HCT and/or post-HCT regimen. Whether imatinib has improved upon HCT in terms of outcomes for children with Ph+ ALL is unclear because the results are mixed.[49–51] There have been very few analyses evaluating HCT outcomes for pediatric Ph+ ALL when comparing patients who receive imatinib versus those who do not. In a report of 37 children who received myeloablative HCT between 1990 and 2006, overall survival (59% versus 58%, $P=0.80$) and disease-free survival (62% versus 53%, $P=0.99$) at 3 years were similar between patients who were treated with imatinib either pre-HCT and/or post-HCT (n=13) and those who did not receive imatinib (n=24).[49] In another study of children randomized to imatinib prior to HCT, 37 children received imatinib compared with 32 who went to HCT without prior treatment with imatinib.[51] The outcomes of HCT were similar between the two groups, with a 4-year disease-free survival of 72.9% for imatinib patients compared with 61.7% for those not receiving imatinib pre-HCT ($P=0.24$). Further, the cumulative incidence of relapse at 4 years was not different between patients treated with imatinib and those who were not (21.2% versus 34.4%, respectively, $P=0.21$).

In summary, imatinib has become the standard of care for treatment of children, adolescents, and young adults with Ph+ ALL, but whether patients proceed to HCT or not remains a matter of debate. Further, the role of prophylactic imatinib post-HCT has yet to be determined in children, but it appears that this may improve post-HCT outcomes when used in adults with this disease.[52–54]

Late effects of imatinib therapy in children

Imatinib is a potent and specific inhibitor of the tyrosine kinase receptor involving the *BCR-ABL1* fusion protein mutated in Ph+ leukemia. Despite the relative specificity of imatinib, off-target effects on related pathways (ie, *c-fms*, *c-kit*, *NADPH*, *hCAII*, and *PDGFR-α*) can occur, and may translate into unexpected toxicities for children treated with imatinib. Because of this concern, the CML working party for the Société Française des Cancers de l'Enfant conducted a Phase IV study of imatinib in children from 2004 to 2008.[55] This study identified growth retardation in children with CML who had received imatinib for prolonged periods. In the 22 children treated in

this study, there was a decrease in height reported during the first year of therapy with imatinib which was significantly reduced using height standard deviation scores compared with patient height prior to starting imatinib. Affected patients reported a median difference in height standard deviation scores of -0.37 (range -1.09 to $+0.14$, $P<0.0001$) during the study time points. A similar sized pediatric cross-sectional study was conducted for chronic phase CML patients (median age 12.9 years) who had been on imatinib therapy for longer than 6 months.[56] Eighteen children were included in this study. Patients were treated with imatinib for a mean duration of 43.7 ± 32.8 (range 6–89) months. Patient height and weight as well as serum growth hormone levels, insulin like growth factor-1 (IGF-1) and insulin-like growth factor binding protein-3 were collected. Thirty-nine percent of patients were found to be growth hormone-deficient, with 89% having IGF-1 z-scores below the mean and 100% of patients having insulin-like growth factor binding protein-3 levels below the mean. All patients were found to have either growth hormone deficiency, insulin-like growth factor-1 deficiency, or both. There was an inverse correlation between duration of imatinib therapy and the proportionate decrease in height-for-age z-scores. This study, along with other reports regarding the detrimental effect of imatinib on growth and bone metabolism,[57–60] provides further evidence that the off-target effects of imatinib must continue to be collected over longer periods of time so we can better understand how long-term continuous inhibition of *c-ABL1* may impact our patients. This is particularly true for younger children treated with imatinib who may be exposed to these effects prior to puberty when they are skeletally most vulnerable.

In addition to imatinib interfering with normal bone metabolism in children, alterations in bone formation have been associated with imatinib therapy. In a study of 17 children aged 4–17 years with CML treated with imatinib, hyperparathyroidism was observed in 47% of patients and low 25-hydroxyvitamin D_3 levels in 88%.[61] In addition, increased osteocalcin (a marker of new bone formation) was found in 33/57 (58%) serum samples, with a linear decline of -0.30 osteocalcin µg per week ($P=0.04$) seen over the duration of imatinib treatment. The authors concluded that impaired bone formation tended to exceed bone resorption in children on imatinib, which suggests that bone remodeling may be dysregulated by TKIs.

Another organ system where there is potential for concern in children, adolescents, and young adults treated for long durations with imatinib is the cardiovascular system, and specifically the heart. Kerkela et al observed a possible unanticipated

side effect of inhibiting *c-ABL1* with imatinib in a report on ten adult patients (median age 65.5 years) presenting with severe heart failure without an obvious cause while on imatinib therapy.[62] The authors were also able to demonstrate similar cardiotoxicity in mice treated with imatinib which developed left ventricular contractile dysfunction. These findings were quickly followed by evidence that cardiotoxicity attributed to imatinib treatment may be more typically seen in elderly adults who have pre-existing cardiac conditions and not the general adult CML population.[63] Moreover, cardiac toxicity reported after HCT in children or adults does not appear to be increased with imatinib treatment pre-HCT and/or-post HCT, except possibly in older adults with advanced phase CML and in those with pre-existing cardiac conditions.[64]

With the introduction of imatinib for treatment of children with Ph+ leukemia, survival outcomes have dramatically improved compared with the pre-imatinib era.[8,26,65,66] What makes pediatric CML unique and different from the challenges faced in adults, is the duration of therapy predicted for these young patients, who will likely be on imatinib for most of their lives, compared with a decade or two in adults. As the long-term toxicities of imatinib and other TKIs continue to be collected over time and reported, the global impact of these agents on a child's growth, general health, and quality of life will become clearer.

Conclusion

Imatinib was the first small molecule inhibitor to have a meaningful impact on treatment outcomes for children and adults with CML or Ph+ ALL. Imatinib has since become the "poster child" of what oncology drug development aims for, ie, a single agent, taken once daily by mouth, and effective as a cancer therapeutic. Although imatinib has become the standard of care for children, adolescents, and young adults with CML or Ph+ ALL, there is still much to be learned, particularly surrounding long-term toxicities in CML, where treatment duration is currently indefinite. The late consequences of both expected and unexpected long-term toxicities in children treated with imatinib remain largely unknown, and will require decades of follow-up for these patients. What is currently known is that long-term use of imatinib detrimentally affects bone formation and metabolism in prepubertal children, but whether or not this translates into clinical significance is unclear.

In summary, imatinib therapy has essentially replaced HCT in children, adolescents, and young adults with CML or Ph+ ALL and dramatically improved outcomes in both diseases. The long-term toxicities of imatinib therapy in

these patients remain largely unknown and further reports with much longer patient follow-up are awaited. As second-generation TKIs such as dasatinib and nilotinib, which may be more potent and effective than imatinib, continue to be used in pediatric Ph+ leukemias, sometimes as first-line agents, the ultimate role of imatinib for treatment of these diseases will become clearer.

Disclosure

The author indicates no potential conflicts of interest in this work.

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