Imatinib mesylate (STI571) for treatment of children with Philadelphia chromosome–positive leukemia: results from a Children's Oncology Group phase 1 study

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The purpose of this study was to determine dose-limiting toxicities and pharmacokinetics of imatinib in children with refractory or recurrent Philadelphia chromosome–positive (Ph+) leukemias. Oral imatinib was administered daily at dose levels ranging from 260 to 570 mg/m². Plasma pharmacokinetic studies were performed on days 1 and 8 of course 1. There were 31 children who received 479 courses of imatinib. The most common toxicities encountered, which occurred in less than 5% of courses, were grade 1 or 2 nausea, vomiting, fatigue, diarrhea, and reversible increases in serum transaminases. One patient at the 440-mg/m² dose level had dose-limiting weight gain. There were no other first-course dose-limiting toxicities. A maximum tolerated dosage was not defined. Among 12 chronic myeloid leukemia (CML) patients evaluable for cytogenetic response, 10 had a complete response and 1 had a partial response. Among 10 acute lymphoblastic leukemia (ALL) patients evaluable for morphologic response, 7 achieved an M1 and 1 achieved an M2 bone marrow. We observed marked interpatient variability in the pharmacokinetic parameters. In conclusion, we found that daily oral imatinib is well tolerated in children at doses ranging from 260 to 570 mg/m². Doses of 260 and 340 mg/m² provide systemic exposures similar to those of adults who are treated with daily doses of 400 and 600 mg, respectively. (Blood. 2004;104: 2655-2660)

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Introduction

Philadelphia chromosome–positive (Ph+) leukemias in children include essentially all chronic myeloid leukemias (CMLs) and 2% to 3% of childhood acute lymphoblastic leukemias (ALLs). Although childhood CML is rare, representing only 2% of childhood leukemias, it is Ph+ in more than 95% of cases.[1] The molecular features, clinical presentation, and response of childhood CML to standard therapies are comparable with adult CML. Although treatments such as hydroxyurea and interferon alpha (IFN α), with or without cytarabine, may induce responses, they are not curative.[2] Similar to adult CML, the only potentially curative therapy for childhood Ph+ leukemias remains allogeneic stem cell transplantation, which is most effective with a matched sibling donor during the chronic phase of CML.[3-7] Unfortunately, high rates of transplant-related mortality (approximately 20%) and posttransplantation recurrence (17%) may occur.[4] The prognosis for children with Ph+ ALL is somewhat worse than for those with CML. Their response to therapy is poor and the 7-year estimated survival rate is only 36%.[8] Overall, the treatment of acute and chronic childhood Ph+ leukemias remains unsatisfactory and more effective therapies are needed.

The Ph chromosome, which results from translocation of the *abl* gene on chromosome 9 onto the *bcr* gene on chromosome 22, leads to constitutive expression of an *abl* tyrosine kinase, which is implicated as the cause of Ph+ chromosome leukemias.[9-13] Imatinib mesylate (imatinib, CGP57148B, STI571), a selective inhibitor of this abnormal *bcr-abl* protein tyrosine kinase, has dramatically changed the treatment of adult Ph+ CML.[14,15] The substantial antileukemic activity of imatinib in adult CML trials prompted investigators in the Children's Oncology Group (COG) to evaluate this agent in children with recurrent or refractory Ph+ leukemias. The objectives of this phase 1 study were to determine the optimal dose of imatinib for phase 2/3 pediatric trials, to evaluate the toxicities and plasma pharmacokinetics of imatinib in children, and to provide a preliminary evaluation of the antileukemic activity of imatinib in Ph+ childhood leukemias.

Patients, materials, and methods

Inclusion and exclusion criteria

Patients younger than 22 years at enrollment who had recurrent or refractory Ph+ leukemia (CML, ALL, or acute myeloid leukemia [AML]) were eligible for this study (P9973). Patients with CML had to have demonstrated resistance to IFN therapy, defined as (1) a white

blood cell (WBC) count 20×10^9/L or higher despite at least 3 months of an IFN-containing regimen, (2) a rising WBC count ($\geq 100\%$ increase and to a level $\geq 20 \times 10^6$/mL confirmed by 2 samples taken at least 2 weeks apart) while receiving an IFN-containing regimen, (3) bone marrow cytogenetics showing 66% or more Ph$^+$ cells after 1 year of IFN therapy, or (4) a 30% or more increase in Ph$^+$ bone marrow cells after an IFN-induced cytogenetic response while receiving IFN therapy.

Other eligibility criteria included (1) an adequate performance status (Karnofsky or Lansky score $\geq 50\%$), (2) a life expectancy of 8 or more weeks, (3) adequate hepatic function (total bilirubin < 1.5 normal for age, alanine aminotransferase [ALT] < 3 times normal for age, and albumin > 20 g/L [2 g/dL]), and (4) adequate renal function (serum creatinine < 1.5 times normal for age or a radioisotope GFR > 70 mL/min/1.73 m^2). Patients had to have fully recovered from acute toxic effects of prior chemotherapy, immunotherapy, and hematopoietic stem cell transplantation. For patients with prior stem cell transplantations, more than 3 months had to have elapsed since completion of the pretransplantation conditioning regimen. Patients were ineligible if they were pregnant or breastfeeding, had an uncontrolled infection, or were receiving another investigational agent. Concomitant anticonvulsant medication was not allowed because of the potential for an interaction between such medications and imatinib.

The Research Ethics Board of each participating institution approved the protocol before enrollment. Patients or their legal guardians gave written informed consent in accordance with the Declaration of Helsinki. Patients also gave assent when appropriate.

Drug administration

Imatinib mesylate was supplied as 50- and 100-mg capsules (Novartis Pharmaceuticals, East Hanover, NJ). Individual patient dosages were rounded to the nearest 50-mg increment. Doses of 800 mg or more per day were given twice daily in 2 equal parts, based on improved tolerance of twice-daily dosing in adults. Imatinib is a local irritant, so we recommended it be taken with water (250 mL; at least 120 mL for children ≤ 3 years old) and food at approximately the same time each day. For patients who could not swallow whole capsules, capsule contents were dissolved in water or apple juice. (In vitro physical stability data indicated that the dissolved content of the capsules remained stable in water and apple juice, but not in orange juice, cola, or milk [B. P., unpublished data, April 2000].) If a patient vomited after taking capsules, the dose was repeated only if capsules were seen and counted. For those who received dissolved drug, the dose was replaced only if the emesis occurred directly after swallowing, appeared to be a substantial amount, or contained evidence of yellow drug.

Imatinib was administered daily. A course of imatinib therapy was defined as a consecutive 28-day interval. There was no break between courses. The starting dosage of 260 mg/m^2 daily was extrapolated from the efficacious 400-mg dosage (equivalent to 235-mg/m^2 daily for an adult with a body surface area of 1.7 m^2) in adults with CML.[16] The imatinib dosage in subsequent cohorts was escalated in approximate 30% increments from 260 to 340, 440, and 570 mg/m^2 daily.

Appropriate antibiotics, blood products, and general supportive care were used as indicated clinically. Patients were required to discontinue concomitant medications known to affect gastric pH (eg, H2 blockers or proton pump inhibitors) 24 hours before study drug administration. Avoidance of medications known to interfere with P-450 metabolism, specifically with the CYP 3A4 and 3A5 isoenzymes, also was recommended.

Trial design

At least 3 patients were entered at each dose level. The dose level was expanded to a maximum of 6 patients if 1 had dose-limiting toxicity (DLT) during the first course (refer to following section for definition of DLT). The maximum tolerated dose (MTD) was defined as the level immediately below the level at which 2 patients in a cohort of no more than 6 had DLT. We planned to stop dose escalations at 570 mg/m^2 (equivalent to 1000 mg in a 1.7-m^2 adult) even if no formal MTD was

identified, due to the lack of experience at higher dosage levels in adults. The protocol was amended to expand enrollment to at least 8 patients, each of whom was evaluable for pharmacokinetics, at the 340-mg/m^2 and 440-mg/m^2 dosages. Our rationale was to enroll sufficient patients to decrease the expected standard error of the mean of the estimated pharmacokinetic parameters 2-fold and more accurately describe the relationship between dose and relevant pharmacokinetic parameters. It was calculated that if 2 of 10 patients enrolled at the 340-mg/m^2 experienced DLT, the 95% confidence interval for the true proportion of patients who experienced DLT would be 0.025 to 0.56. If 1 of 8 patients enrolled at the 440-mg/m^2 experienced DLT, the 95% confidence interval for the true proportion of patients who experienced DLT would be 0.031 to 0.53. For comparison, if 1 of 6 patients enrolled at a dose level experienced DLT, the 95% confidence interval for the true proportion of patients who experienced DLT would have been 0.042 to 0.64.

Definition of dose-limiting toxicity

Adverse events were graded according to Common Toxicity Criteria (CTC) Version 2.0 for Toxicity and Performance Reporting (National Cancer Institute; http://ctep.info.nih.gov/reporting/index.html). Safety assessments consisted of monitoring and recording all adverse events and serious adverse events (severity, duration, outcome, and presumed relationship to study drug), regular monitoring of hematologic parameters, blood chemistry analysis, urinalysis, and regular assessments of vital signs, physical condition, and body weight.

Nonhematologic DLT was defined as any grade 3 or 4 toxicity attributable to the investigational drug with the specific exclusion of grade 3 nausea and vomiting, grade 3 elevation of serum transaminases (aspartate aminotransferase [AST] or ALT) that returned to grade 1 or below before the next treatment course, or grade 3 fever or infection. A grade 2 or higher adverse event that caused a 7-day or longer interruption during course 1 was also considered dose limiting. Imatinib was withheld if a grade 2 nonhematologic adverse event failed to resolve with supportive therapy or if there was a grade 3 or 4 nonhematologic adverse event. Imatinib was resumed at one dosage level lower (30% lower if at the first dosage level) upon resolution to a grade 1 or lower of the adverse event.

Hematologic DLT was defined as the failure to recover a peripheral blood absolute neutrophil count (ANC) to higher than 500×10^6/L and a platelet count to higher than 20×10^9/L within 5 weeks from the first day of a course due to bone marrow aplasia, and not to malignant infiltration or fibrosis of marrow. There were no imatinib dosage modifications for hematologic adverse events during the first 28 days; however, for grade 4 hematologic toxicity, drug was withheld until ANC was higher than 1000×10^6/L. Imatinib was resumed at the same dose if marrow cellularity was 10% or more. Dosage was reduced 30% if grade 4 neutropenia recurred or if it was associated with marrow cellularity of less than 10%, marrow fibrosis, or a marrow blast count of more than 30%.

Analyzable populations

The safety-analyzable population included patients who received at least 1 dose of study medication and patients who received treatment according to protocol for at least the first course, or until discontinuation due to unacceptable toxicity. This population was used to determine the MTD or dosage recommended for further study. The efficacy-evaluable population included patients who received at least one dose of study medication and for whom there was at least one efficacy evaluation after baseline. For efficacy analyses, 3 different patient subsets were considered because of markedly differing outcomes, those with chronic-phase CML (CML-CP), and those with acute leukemias of either myeloid phenotype (CML in blast crisis or AML, otherwise described as advanced myeloid leukemias) or lymphoid phenotype (ALL or CML blast crisis, otherwise described as advanced lymphoid leukemias).

Efficacy evaluation

Criteria for response. Antileukemic efficacy was assessed by monitoring peripheral WBC counts, bone marrow blast counts, and bone marrow cytogenetic studies. Efficacy evaluations were performed at the completion of each imatinib course for the first 3 courses, then every 4 months or as indicated clinically.

Cytogenetic response. Cytogenetic response was expressed in terms of the ratio of number of Ph+ metaphases in bone marrow divided by initial number of Ph+ metaphases and categorized as follows: (1) complete response, 0% Ph+ cells; (2) partial response, more than 0% to 35% or less Ph+ cells; (3) minor response, more than 35% to 65% or less Ph+ cells; (4) minimal response, more than 65% to 95% or less Ph+ cells; and (5) no response, more than 95% Ph+ cells.

Morphologic response in acute leukemia patients. Morphologic response in advanced lymphoid leukemia or advanced myeloid leukemia was defined as follows: (1) M1, 0% to 5% bone marrow blast cells; (2) M2, more than 5% to 25% bone marrow blast cells; or (3) M3, more than 25% bone marrow blast cells.

Hematologic response for chronic-phase CML. A complete hematologic response (CHR) for a patient with chronic-phase CML was defined as WBC count less than $10\,000 \times 10^6$/mL and a platelet count less than 450×10^9/mL. Documentation of an increase above these values for 4 consecutive weeks was considered a recurrence.

Overall survival

Overall survival was defined as time from first dose of imatinib to death. Life status current to October 2003 was considered in this analysis. Patients who were alive at last contact were censored at that time.

Distribution functions for time in CHR and overall survival were estimated by the method of Kaplan and Meier[17] using all relevant patients regardless of dose level assigned. Confidence intervals (CIs) for distribution function were calculated by transforming the CI for the logarithm of the estimate of the survivor function.

Pharmacokinetic evaluation

Blood samples for assessment of pharmacokinetic parameters of imatinib were collected on days 1 and 8 during course 1. Patients who participated in the pharmacokinetic studies did not receive imatinib on day 9 of course 1 so that the elimination half-life could be adequately characterized. Blood samples were collected immediately before drug administration on day 1 and day 8 of course 1 and at 0.5, 1, 1.5, 2, 4, 8, and 24 hours after drug administration for once-daily dosing (total daily dose < 800 mg). Samples were placed in heparinized tubes and centrifuged at 5000*g* for at least 10 minutes. Plasma was separated and stored at −20°C or below until analysis.

Plasma concentrations of imatinib were measured using a validated high-performance liquid chromatography–mass spectrometry–mass spectrometry (LC/MS/MS) method. Assays were performed at Novartis Pharmaceuticals.[18] Noncompartmental pharmacokinetic parameters were calculated from plasma concentration–time profiles of imatinib and CGP 74588 using WinNonlin Pro 3.2 (Pharsight, Mountain View, CA).

Results

Between February 2000 and September 2001, 31 eligible patients were enrolled at 23 participating COG centers (list available upon request). Diagnoses were chronic-phase CML (CML-CP) in 14 patients, advanced myeloid leukemias in 7 patients (1 AML and 6 blast-crisis CML), and advanced lymphoid leukemias in 10 patients (9 ALL and 1 biphenotypic leukemia). The median patient age at initial diagnosis was 12 years (range, 1-17 years). The median age at study entry was 14 years (range, 3-20 years). There were 23 men (74%) and 8 women (26%). Of the patients, two thirds had received multiagent systemic chemotherapy and 13 patients had had a prior hematopoietic stem cell transplantation.

There were 2 patients excluded from the analysis of morphologic response for the following reasons: (1) drug was discontinued in one patient with AML who was in hematologic remission at study entry after 15 weeks of imatinib to facilitate bone marrow transplantation, and (2) the other patient had only extramedullary disease involvement at study enrollment and was therefore inevaluable for morphologic response.

At the time of these analyses, 479 total courses of imatinib had been administered. Most patients received daily drug without interruption, although 3 chronic-phase CML patients and 4 advanced leukemia patients had treatment interruptions for at least 14 consecutive days following completion of course 1. Dose reductions following adverse events were made according to protocol guidelines in 7 chronic and 3 advanced leukemia patients. Of the patients, 16 received imatinib for at least 6 months and 8 (2 per dosage cohort), for at least 12 months (Table 1).

Safety and toxicity

The most common reported adverse events (incidence over all courses) were nausea (4%), vomiting (3.5%), fatigue (lethargy, malaise, asthenia; 3.5%), increased AST (3.8%) or ALT (2.9%), and diarrhea (2.7%). These events were mostly grade 1 or 2, except for one episode of grade 3 vomiting and 4 occurrences of grade 3 ALT elevations. Of note, the incidence of arthralgia/myalgia was 1.5% and edema/weight gain less than 1%. There was only one episode of a first-course DLT, which was a grade 2 weight gain (10% increase from 71.4 to 78.6 kg) without clinical evidence of edema in a patient treated at the 440-mg/m² dose level. There were no other first-course DLTs; therefore, an MTD was not defined. Additional dose-limiting adverse events reported in subsequent courses are summarized here. These adverse events, which are typical of events that occur during the treatment and management of patients with acute leukemias, were infrequent, occurring in only 15 (< 5%) of 479 courses.

The relationship attribution to imatinib of dose-limiting adverse events that occurred after course 1 was not always readily discerned. For example, one patient with chronic-phase CML in cytogenetic relapse after stem cell transplantation developed a pericardial effusion associated with pericarditis after almost 3 months of imatinib (340 mg/m² dosage). Since this patient also reverted to full donor chimerism, it is not clear whether it was drug related or a result of graft-versus-host disease from the prior bone marrow transplantation. Another patient with grade 4 thrombocytopenia, who was receiving concomitant low-molecular-weight heparin, had an intracranial hemorrhage during the second course of imatinib therapy (260-mg/m² dosage). The relationship of this adverse event to

Table 1. Number of courses delivered according to assigned treatment regimen

	Number of courses administered				
	260 mg/m²	340 mg/m²	440 mg/m²	570 mg/m²	All doses
No. of patients	6	11	8	6	31
Median	3.5	7	17.5	4	6
Range	2-46	1-42	2-40	2-38	1-46

mg/m² indicates milligram per square meter.

imatinib is not clear. At the 340-mg/m^2 dose level, other grade 3 or 4 dose-limiting adverse events, which occurred in 7 of 164 courses, included hypotension (1 event), infection without neutropenia (1 event), and seizures (5 events, 1 patient). At the 440-mg/m^2 dosage, other dose-limiting grade 3 or 4 adverse events that occurred in 3 of 149 courses included weight gain, edema, and pericardial effusion as previously discussed. At the 570-mg/m^2 dose level, grade 3 or 4 dose-limiting adverse events that occurred in 5 of 80 courses included 2 catheter-related infections, 1 episode of hypotension, and 2 episodes of neutropenia. There was no apparent relationship between administered dose and incidence or type of adverse events in the limited number of patients treated on this phase 1 clinical trial.

Pharmacokinetic results

Imatinib pharmacokinetic data for day 1, course 1, were available for 22 patients. Data for 5 patients who received twice-daily imatinib were excluded from the day-1 pharmacokinetic (PK) analysis. Imatinib was detectable in plasma 30 minutes after dosing (the first sampling time). The maximum mean plasma concentrations (C_{max}) ranged from 3624 ng/mL (at 260 mg/m^2) to 8538 ng/mL (at 570 mg/m^2) after once-daily administration. The day-1 imatinib PK parameters derived from the plasma concentration versus time data are summarized in Table 2. There was substantial interpatient variability in PK parameters.

PK parameters were also evaluated after 7 days, by which time plasma concentrations had reached steady state. Data were available for 22 patients receiving once-daily dosage. The day-8 area under the curve (AUC)$_{(0-24h)}$ at steady state for patients who received once-daily dosing at 340 mg/m^2 was 1.7 times higher than the day-1 AUC$_{(0-24h)}$ (data not shown). Similar to day 1, there was considerable interpatient variance in the PK parameters. The coefficient of variation (CV) for AUC$_{(0-24h)}$ at steady state ranged from 21% (260 mg/m^2) to 68% (570 mg/m^2). The expression of dose as milligram per kilogram of body weight did not reduce interpatient variance. Mean apparent total clearance of drug in the 22 patients included for analysis was 7.7 L/h/m^2 ± 4.6 (data not shown).

Plasma concentrations at steady state (Figure 1A) and day-1 mean AUC (Figure 1B) in children after once-daily doses of 260 mg/m^2 and 340 mg/m^2 were comparable with the values reported in adults given daily doses of 400 mg ($\sim$ 235 mg/m^2) and 600 mg ($\sim$ 350 mg/m^2), respectively.[19] Pharmacodynamic effects were explored by examining the relationship between WBC counts after 1-month treatment and drug exposure (both AUC$_{(0-24h)}$ and AUC$_{(0-\infty)}$). Within the dose range of this study, there was no correlation between drug exposure and WBC count (data not shown).
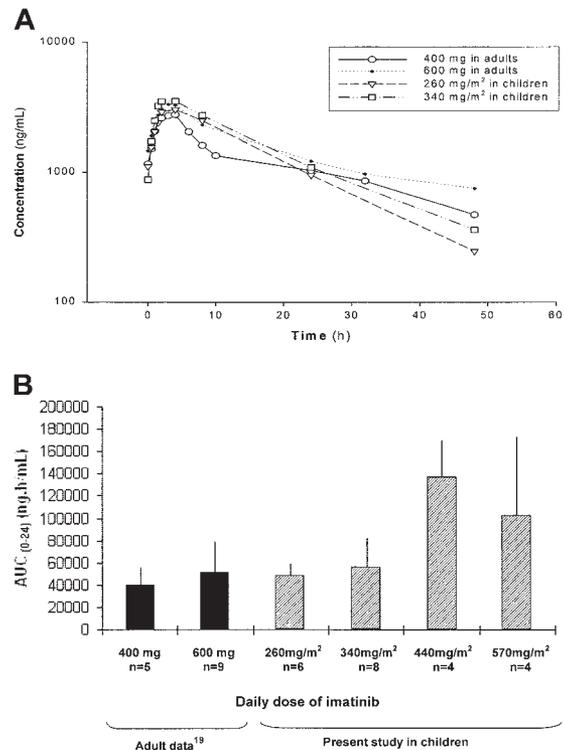

Figure 1. Pharmacokinetic results. (A) Mean plasma concentration versus time curves for imatinib at steady state in children and adults. Data for adults are from Peng et al.[19] h indicates hour; ng/mL, nanogram per milliliter; and mg/m^2, milligram per square meter. (B) Comparison of the imatinib AUCs at steady state in children and adults. Note: A 400-mg dose in adults is approximately 235 mg/m^2 and a 600-mg dose is approximately 350 mg/m^2. Data for adults are from Peng et al.[19] AUC$_{(0-24h)}$ (ng.h/mL) indicates area-under-the concentration-time curve, from time 0 to 24 hours (nanogram times hour per milliliter); mg/m^2, milligram per square meter; and n, number of patients. Error bars indicate SD.

Response

Chronic-phase CML patients. Hematologic responses were assessed in 14 chronic-phase CML patients, all with elevated WBC or platelet counts at baseline. Complete hematologic responses occurred in all 14 patients within 7 to 30 days after beginning imatinib treatment. The Kaplan-Meier estimate for the 2-year probability of continuous complete hematologic response for this group was 92% (95% CI: 57%-99%). One patient who had a 2-week interruption of therapy for neutropenia met the criteria for hematologic recurrence on day 112, with a minimally elevated WBC count and later with elevated platelet counts. However, the patient subsequently achieved a second complete hematologic response and partial cytogenetic response after reinitiation of imatinib therapy.

Cytogenetic response data, assessed by standard marrow cytogenetics, were available for 12 of 14 evaluable chronic-phase CML patients. Median follow-up for evaluation of

Table 2. PK parameters (mean ± standard deviation) of imatinib mesylate in patients on day 1

Dose/day, mg/m^2	No. of patients	t_{max}, h	C_{max}, µg/mL	$T_{1/2}$, h	AUC$_{(0-24 h)}$, µg.h/mL	AUC$_{(0-\infty)}$, µg.h/mL	Vz/F, L	Cl/F, L/h
260	6	3.5 ± 2.5	3.6 ± 2.0	8.9 ± 1.2	51.0 ± 34.9	60.6 ± 4.0	119 ± 83	8.9 ± 5.8
340	8	3.7 ± 2.1	2.5 ± 0.9	9.2 ± 1.9	32.1 ± 13.0	39.6 ± 17.4	167 ± 84	12.8 ± 6.8
440	4	5.0 ± 2.0	5.4 ± 4.3	12.8 ± 2.5	76.1 ± 54.8	103.3 ± 64.8	190 ± 213	9.3 ± 9.4
570	4	2.9 ± 1.3	8.5 ± 9.2	14.8 ± 12.9	106.7 ± 113.6	150.7 ± 133.1	109 ± 88	5.6 ± 2.8

PK indicates pharmacokinetics; mg/m^2, milligram per square meter; No., number; t_{max}, h, time to reach C_{max} (hours); C_{max}, µg/mL, maximum mean plasma concentrations (microgram per milliliter); $t_{1/2}$, h, half-life (hours); AUC$_{(0-24h)}$, µg.h/mL, area-under-the concentration-time curve, from time 0 to 24 hours (microgram times hour per milliliter); AUC$_{(0-\infty)}$, µg.h/mL, area-under-the concentration-time curve, from time 0 to infinity (microgram times hour per milliliter); Vz/F, L, apparent volume of distribution during terminal phase after oral intake (liter); and Cl/F, L/h, apparent total plasma clearance of drug after oral intake (liter per hour).

cytogenetic response was 13 courses (range, 2-30 courses). Of the patients, 10 (83%) achieved complete cytogenetic responses (CCRs), confirmed by second consecutive cytogenetic evaluations after at least one additional course in 8 patients (62%). Median time to CCR was 3 months (range, 2-6 months). There were 2 patients in continuous CCR who developed new cytogenetic abnormalities in Ph− cells, 1 after 16 and 1 after 29 courses of treatment. These abnormalities, which were not initially reported in the Ph[+] clones, consisted of a t(3;11)(p21; p15) in 4 metaphases in one patient and a t(20;21) (q11.2;22.3) in 5% of metaphases in the other. No evidence of progressive disease was reported in either patient after completion of 25 and 45 courses. In subsequent cytogenetic evaluations, 2 other patients with initial CCRs showed evidence of recurrence of Ph^{+} cells. The first and second had Ph[+] metaphases in 5% and 15% of analyzed metaphases after 12 and 15 courses of imatinib, respectively. This patient reverted to a normal karyotype from the 19th through 24th courses. However, the karyotype was again Ph[+] at the course-28 evaluation, with 20% Ph^{+} cells associated with other clonal cytogenetic anomalies. A second patient developed 3% Ph^{+} cells after the ninth course. Subsequent evaluation by fluorescence in situ hybridization (FISH) analysis at initiation of the 30th course did not find Ph^{+} cells. One additional patient achieved a partial cytogenetic response after completing 17 courses. Interestingly, this response was associated with new complex chromosomal abnormalities.

Advanced leukemia patients. Among the 7 patients with myeloid phenotype, 6 were evaluable for response, and 2 (33%) achieved M1 responses. Among the 10 patients with lymphoid phenotype, 7 (70%) achieved M1 marrow responses and 1 (10%) achieved an M2 response.

Overall survival

At the time of this analysis, of the 14 patients with chronic-phase CML 13 were alive and 1 died. The death, which occurred while in remission, was a result of complications following a stem cell transplantation. The estimated median survival for patients with chronic CML exceeds 24 months. For patients with advanced leukemia, the estimated median survival is 7 months for those with myeloid phenotype and 15 months for those with lymphoid phenotype (Figure 2). Of the patients, 11 with advanced myeloid or lymphoid leukemias died with evidence of refractory or recurrent disease; 2 additional patients died of disease recurrence following stem cell transplantation. In addition to the chronic-phase CML patient mentioned above, 2 other

patients have died of transplant-related mortality without documentation of recurrence of disease. There are 2 patients with advanced leukemia currently alive, 1 in continuous remission 20 months following stem cell transplantation, while the other was alive in relapse at time of last evaluation.

Discussion

In this trial we demonstrated that imatinib is well tolerated in children with recurrent or refractory Ph[+] leukemias at doses ranging from 260 mg/m^2 to 570 mg/m^2. Escalation to an MTD was not pursued since there was an overall high response rate following imatinib treatment at doses comparable with or exceeding those routinely used in adults with Ph[+] leukemias. Data from several adult phase 2 studies suggest that a dose of 600 mg ($\sim$ 350 mg/m^2) is more effective for patients with advanced Ph[+] leukemias than the recommended dose of 400 mg ($\sim$ 235 mg/m^2) for chronic-phase CML.[20,21] In addition, results from a recent single-center adult phase 2 study suggest that higher doses of imatinib, 800 mg/d ($\sim$ 570 mg/m^2), may be associated with faster onset and higher rate of cytogenetic response.[22] Based on these results, the recommended doses for subsequent evaluation in the pediatric population are 260 mg/m^2 and 340 mg/m^2, which are comparable with the current recommended fixed dosages of 400 mg for adults with chronic-phase CML and 600 mg for adults with advanced Ph[+] leukemias. However, doses as high as 570 mg/m^2, which do not exceed the pediatric MTD, were well tolerated and may also be potentially used in future studies.

In this trial, all evaluable patients with Ph[+] chronic-phase CML achieved a complete hematologic response, 83% of whom had a CCR. The majority of CCRs were sustained and, at the time of this report, only 2 patients had experienced cytogenetic recurrences. These results compare favorably with the 41% CCR reported in a large phase 2 trial of 454 adult patients with IFN refractory chronic-phase CML.[23] In that study, attainment of a cytogenetic response was associated with statistically significant prolongation of progression-free survival.

The response assessment criteria for children with advanced Ph[+] leukemias enrolled in this trial were based on bone marrow morphology. The observed response rates of 33% in children with myeloid phenotype and 70% in children with lymphoid phenotype following imatinib administration are similar to reported response rates in adults with advanced leukemias.[20,24-25] The median duration of survival was 7 months for patients with myeloid phenotype and 15 months for those with lymphoid phenotype. These findings suggest that imatinib may provide a bridge to subsequent allogeneic bone marrow transplantation for patients with suitable donors. In addition, future studies in children with acute Ph[+] leukemias that evaluate imatinib in combination with established multiagent chemotherapy regimens may provide even more effective bridging therapies.

Similar to adults, there was marked interpatient variability in the observed pharmacokinetic parameters of imatinib in children.[19] To compare pediatric with adult data, we evaluated the apparent clearance of imatinib. As clearance is independent of dose, we calculated one clearance value for all children for all dose levels. Mean apparent total clearance of drug in 22 pediatric patients, corrected for a surface area of 1.7 m^2, is comparable with the reported average value of about 14 L/h in adults.[19] The activity of
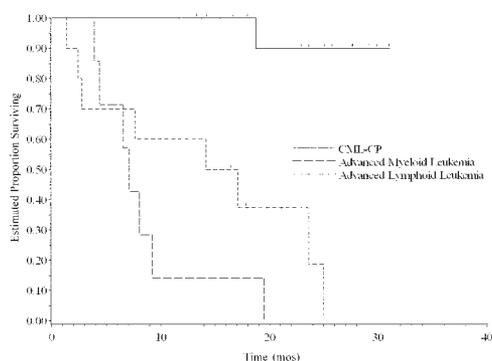

Figure 2. Overall survival from study enrollment by type of leukemia. CML-CP indicates chronic myelogenous leukemia–chronic phase.

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CYP3A, one of the major enzymes responsible for the biotransformation of imatinib, in the general population is highly variable (4- to 5-fold).[26] This variability may have contributed to the observed interpatient differences in imatinib pharmacokinetics. Variations in protein (particularly albumin) levels, possibly related to nutritional status, may have also contributed to the observed interpatient variability in imatinib disposition.

In summary, daily imatinib doses of 260 to 570 mg/m^2 are safe and effective in children with Ph$^+$ leukemias. Although hematopoietic stem cell transplantation remains the treatment of choice for children with Ph$^+$ leukemias whose physiologic state permits intensive therapy and for whom donors are available, imatinib mesylate is an important option for facilitating induction of complete remission in children with recurrent or refractory disease or for whom there is not a suitable donor. On the basis of the results of our study and the favorable results obtained with newly diagnosed adult patients with CML,[27] the COG is currently evaluating the role of imatinib in children with newly diagnosed Ph$^+$ CML.

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Appendix

The table lists the treatment institutes and the number of patients treated per institute.

Institute	Number of Patients
Emory University	2
M.D. Anderson Cancer Center	1
Midwest Children's Cancer Center	2
Stanford University	1
St Jude Children's Hospital	1
Cook Children's Medical Center	1
Boston Floating Hospital	2
Children's Memorial Hospital (Chicago)	1
Hôpital Sainte-Justine	2
University of Texas at San Antonio	1
Children's Hospital and Medical Center	1
Children's Hospital Los Angeles	2
Children's Hospital Medical Center Cincinnati	1
Children's Hospital of Orange County	1
Children's Hospital of Philadelphia	1
Indiana University Riley Hospital for Children	1
Memorial Sloan-Kettering Cancer Center	2
Princess Margaret Hospital for Children	1
University of California Los Angeles School of Medicine	1
University of Minnesota Hospital & Clinic	2
University of Mississippi Medical Center	1
Duke University	1
University of Florida	2

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Imatinib mesylate (STI571) for treatment of children with Philadelphia chromosome-positive leukemia: results from a Children's Oncology Group phase 1 study

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