Pediatric Phase I Trial and Pharmacokinetic Study of Dasatinib: A Report From the Children's Oncology Group Phase I Consortium

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ABSTRACT

Purpose

Dasatinib is an orally available tyrosine kinase inhibitor with low nanomolar activity against SRC family kinases, BCR-ABL, c-KIT, EPHA2, and the PDGF- β receptor. Dasatinib was found to have selective activity in several tumor models in the Pediatric Preclinical Testing Program.

Patients and Methods

A phase I study of dasatinib in pediatric patients with refractory solid tumors or imatinib-refractory, Philadelphia chromosome-positive leukemia was performed. Dose levels of 50, 65, 85, and 110 mg/m²/dose, administered orally twice daily for 28 days, with courses repeated without interruption, were studied. Pharmacokinetic studies were performed with the initial dose.

Results

A total of 39 patients (solid tumors, n = 28; chronic myeloid leukemia [CML], n = 9; acute lymphoblastic leukemia, n = 2) were enrolled. No dose-limiting toxicities (DLTs) were observed at the 50, 65, and 85 mg/m² dose levels. At 110 mg/m², two of six patients experienced DLT including grade 2 diarrhea and headache. In children with leukemia, grade 4 hypokalemia (50 mg/m²), grade 3 diarrhea (85 mg/m²), and grade 2 creatinine elevation (50 mg/m²) were observed. DLT in later courses included pleural effusions, hemangiomatosis, and GI hemorrhage. There were three complete cytogenetic responses, three partial cytogenetic responses, and two partial/minimal cytogenetic responses observed in evaluable patients with CML.

Conclusion

Overall, drug disposition and tolerability of dasatinib were similar to those observed in adult patients.

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INTRODUCTION

Dasatinib is currently approved for the treatment of adults with chronic-, accelerated-, or blast-phase chronic myeloid leukemia (CML) or adults with Philadelphia chromosome (Ph)-positive acute lymphoblastic leukemia, with resistance or intolerance to prior therapy. Through competitive inhibition of adenosine triphosphate binding sites,¹ dasatinib inhibits multiple tyrosine kinases including BCR-ABL, SRC family kinases, c-KIT, EPHA2, and PDGF- β receptor. Dasatinib also inhibits tyrosine kinases that have been rendered insensitive to imatinib as a result of mutations in the tyrosine kinase binding domain.¹ However, dasatinib, like imatinib and other currently available tyrosine kinase inhibitors, is not active against the T3151 BCR-ABL mutation.²

Recently published in vitro studies performed in the Pediatric Preclinical Testing Program demon-

strated that dasatinib had activity at low nanomolar concentrations against a rhabdoid tumor cell line.³ In vivo studies demonstrated a two-fold extension of event-free survival in one of four mouse rhabdoid (KT016) models. Modest antitumor activity in other models, including ependymoma, glioblastoma, and osteosarcoma, was also observed.

Dasatinib can induce both hematologic and cytogenetic responses in adult patients with CML or BCR-ABL-positive acute lymphoblastic leukemia (ALL) refractory to imatinib.⁴⁻⁷ A phase I study in adults with Ph-positive leukemia did not define a maximum-tolerated dose (MTD) for dasatinib⁵; a similar study in adult patients with solid tumors demonstrated a similar toxicity profile.⁸ Common toxicities observed in adult patients include myelosuppression, thrombocytopenia, constitutional complaints, mild electrolyte abnormalities, and effusions.⁵ In adults, daily dosing has been found to be equally efficacious and less toxic than

twice-daily dosing. However, these data were not available at the start of the pediatric phase I trial.

Therefore, we conducted a pediatric phase I trial and pharmacokinetic study of dasatinib. Dasatinib was administered orally twice daily for 28 consecutive days, with courses repeated without interruption in children with relapsed or refractory solid tumors and in select children with imatinib-resistant, Ph-positive leukemia. The trial was conducted by the Children's Oncology Group phase I consortium in 21 treatment centers throughout the United States and Canada.

PATIENTS AND METHODS

Patient Eligibility

Patients with solid tumors refractory to standard therapy or imatinib-resistant, Ph-positive leukemia were eligible for the trial. Eligibility criteria included the following: age 1 to 21 years (inclusive); Karnofsky or Lansky performance score of more than 50; recovery from the acute toxic effects of prior chemotherapy, radiotherapy, or immunotherapy with a minimum elapsed period of at least 7 days since the last dose of corticosteroids or hematopoietic growth factors; at least 3 months since stem-cell transplantation; at least 3 months since prior craniospinal radiation, pelvic radiation, or total-body irradiation; at least 2 weeks since local palliative radiation; and at least 6 weeks since other substantial radiation. Patients could not have evidence of active graft-versus-host disease. Patients were required to have adequate renal function (serum creatinine $<$ the upper limit of normal for age or a glomerular filtration rate $>$ 70 mL/min/1.73 m²), adequate liver function (serum bilirubin $<$ 1.5 mg/dL $\times$ the upper limit of normal for age, ALT $<$ 110 U/L, and albumin $>$ 2 g/dL), adequate cardiac function, and adequate pulmonary function. Patients with solid tumors were required to have an absolute neutrophil count more than 1,000/ μ L, a platelet count more than 100,000/ μ L, and a hemoglobin level more than 8 g/dL. Patients with leukemia were required to have platelet count more than 20,000/ μ L and a hemoglobin level more than 8 g/dL. If necessary, platelet and RBC transfusions were allowed to meet these parameters on both treatment strata. One patient per cohort with bone marrow metastatic disease was permitted on protocol provided that the patient was not refractory to transfusion therapy. Administration of hydroxyurea was permitted up to 24 hours before the start of therapy if needed for cytoreduction of leukemia. Intrathecal therapy was permitted for patients with CNS leukemia.

Exclusion criteria included pregnancy or lactation in women of child-bearing age; uncontrolled infection; receipt of concomitant enzyme-inducing anticonvulsant, antithrombotic, or antiplatelet agents; several CYP3A inhibitors (itraconazole, ketoconazole); HIV-positive patients whose highly active antiretroviral therapy regimen might interact with dasatinib; or concomitant use of other experimental agents.

Institutional review board approval was obtained at participating institutions. Informed consent was obtained from patients age $\geq$ 18 years or from parents/legal guardians of children age less than 18 years (with child assent when appropriate), according to individual institutional policies.

Dosage and Drug Administration

Dasatinib was administered orally twice daily either in tablet form or dissolved in a juice solution (1 oz of double-strength lemonade or preservative-free apple or orange juice).

Trial Design

The dose-finding component of this trial used a standard 3 + 3 dose-escalation design to define the toxicities and determine the MTD in children with relapsed or refractory solid tumors. Children with Ph-positive leukemia were enrolled at one dose level below the dose level under study in patients with solid tumors but were not included in the dose-finding cohorts. The starting study dose was 50 mg/m²/dose administered twice daily with planned escalations to 65, 85, and 110 mg/m²/dose. Courses were 28 days in length with no interruption between courses.

Safety Assessments

The National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0) was used to classify adverse events. Dose-limiting toxicity (DLT) was defined as any grade 3 or 4 adverse event that was possibly, probably, or definitely attributed to dasatinib in the first cycle of treatment. Patients not experiencing DLT during the first cycle must have received at least 85% of the prescribed dose to be considered fully evaluable for toxicity. Grade 2 nonhematologic toxicities were considered dose limiting if the toxicity duration was more than 7 days and necessitated removal from the trial. Patients enrolled onto the Ph-positive leukemia stratum were considered nonevaluable for hematologic toxicity. The following adverse events were excluded as DLTs: grade 3 nausea and vomiting of less than 3 days in duration with appropriate antiemetic therapy; grade 3 transaminases that return to levels that meet initial eligibility criteria within 7 days of study drug interruption and that do not recur on study rechallenge with study drug; grade 3 fever or infection of less than 5 days in duration; and grade 3 hypocalcemia responsive to oral calcium supplementation.

Efficacy Assessments

Response in patients with solid tumors was evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) criteria.⁹ Patients with imatinib-resistant CML were assessed for hematologic and cytogenetic response using standard definitions.¹⁰ Patients with Ph-positive ALL were assessed by bone marrow response as follows: complete response (CR) was defined as an M1 ($<$ 5% blasts) marrow with adequate cellularity; partial response was defined as an M2 (6% to 25% blasts) marrow; progressive disease (PD) was defined as increase of at least 25% in the absolute number of circulating leukemic cells, development of extramedullary disease, increase by $\geq$ 30% in Ph-positive bone marrow cells as assessed by standard cytogenetics, or other laboratory or clinical evidence of PD; and stable disease was defined as response other than a CR, partial response, or PD.

Pharmacokinetic Studies

Plasma pharmacokinetic studies of dasatinib were performed in consenting patients on day 1 of course 1. Plasma samples were obtained at 0, 15, 30, 60, and 90 minutes and 2, 4, 6 to 8, 9 to 12, and 24 to 28 hours after the oral dose, with the day 1 evening dose being withheld to allow for a better estimation of terminal half-life. Plasma samples were assayed for dasatinib using a validated liquid chromatography tandem mass spectrometry method.⁸ The dasatinib and metabolite plasma concentration-time data were analyzed using noncompartmental methods. The peak concentration (C_{max}) and time to peak concentration (T_{max}) were determined from the concentration-time curve for each patient. Area under the concentration curve to the last measured time point (AUC_{0-last}) was calculated with the linear trapezoidal method and extrapolated to infinity ($AUC_{0-\infty}$) by adding the final measured plasma concentration divided by the terminal rate constant, which was derived from the slope of the natural log-transformed concentrations and times on the terminal elimination phase of the decay curve. The half-life was determined by dividing 0.693 by the terminal rate constant, and the apparent clearance was calculated from dose/ $AUC_{0-\infty}$. Pharmacokinetic data past 9 hours were not used because of sparse data.

RESULTS

Patient Characteristics

A total of 39 patients were enrolled onto this trial, all of whom were eligible (Table 1). Twenty-eight patients (median age, 11.7 years; range, 2 to 20.9 years) were enrolled onto the solid tumor stratum, of whom 18 were fully evaluable for toxicity. Reasons for inevaluability were PD before completion of at least one cycle ($n = 4$), physician preference ($n = 2$), and withdrawal of consent for study participation ($n = 4$); none of these patients experienced DLT. Eleven patients (median age, 10 years; range, 2.7 to 17.6 years) were enrolled onto the leukemia stratum, all of whom were fully evaluable for toxicity. Data on *BCR-ABL* mutation status was not available for patients with CML.

Table 1. Demographics and Clinical Characteristics of Eligible Patients

Demographic or Clinical Characteristic	No. of Patients
Age	
Mean	11
SD	5.1
Range	2-20
Sex	
Male	20
Female	19
NAACCR race	
White	28
Black	5
Filipino	1
Asian India, Pakistani	1
Other	2
Unknown	2
NAACCR ethnicity	
Non-Hispanic	32
Mexican (including Chicano)	1
Hispanic, NOS	4
Unknown whether Spanish	2
Prior therapy	
Median, No.	2
Range, No.	0-10
Prior radiation	16
Prior SCT	6
Karnofsky/Lansky performance score	
100	21
90	11
80	4
70	2
60	0
50	1
Diagnosis	
Chronic myelogenous leukemia	9
Osteosarcoma, NOS	
Hepatoblastoma	3
Acute lymphoblastic leukemia	2
Alveolar rhabdomyosarcoma	2
Synovial sarcoma, NOS	2
Ewing sarcoma	2
Neuroblastoma, NOS	2
Carcinoma, NOS	1
Adenocarcinoma, metastatic, NOS	1
Neuroendocrine carcinoma, NOS	1
Renal cell carcinoma, NOS (C64.9)	1
Paraganglioma, NOS	1
Desmoplastic small round cell tumor	1
Leiomyosarcoma, NOS	1
Rhabdomyosarcoma, NOS	1
Nephroblastoma, NOS	1
Malignant rhabdoid tumor	1
Malignant myoepithelioma	1
Epithelioid hemangioendothelioma, malignant	1
Telangiectatic osteosarcoma	1

Abbreviations: SD, standard deviation; NAACCR, North American Association of Central Cancer Registries; NOS, not otherwise specified; SCT, stem-cell transplantation.

Table 2. DLTs in Course 1

Dose Level (mg/m ²)	No. of Patients Entered	No. of Evaluable Patients	No. of Patients With DLT	DLT Description
Solid tumor stratum				
50	4	3	0	NA
65	6	3	0	NA
85	7	6	1	Headache
110	11	6	2	Headache, diarrhea
Leukemia stratum				
50	3	3	1	Hypokalemia
65	2	2	0	NA
85	6	6	2	Rash, diarrhea
110	0	0	0	NA

Abbreviations: DLT, dose-limiting toxicity; NA, not applicable.

headache that led to withdrawal from the study, and a 16-year-old girl with adenoid cystic carcinoma developed grade 2 diarrhea that was considered dose limiting. The headache and diarrhea resolved within 24 and 72 hours, respectively, of study drug discontinuation. Three other patients enrolled onto the solid tumor stratum at 110 mg/m²/dose experienced DLTs in subsequent courses, including development of grade 2 pleural effusions (n = 2), grade 3 chest pain (n = 1), and grade 3 pruritic, maculopapular rash (n = 1; Table 3). All toxicities reported are listed in Appendix Tables A1 and A2 (online only).

Although defining a separate MTD in the leukemia stratum was not an objective of the protocol, a number of toxicities were observed during the first and subsequent courses (Tables 2 and 3). One patient, a 3-year-old boy with recurrent CML after stem-cell transplantation, developed hemangiomatosis with a grade 3 GI hemorrhage during course 5 at the 65 mg/m²/dose level. These events were preceded by *Escherichia coli* H0157:H1 gastroenteritis 1 month before. Dasatinib was held, and the patient was treated with corticosteroids for a total of 4 weeks. Repeat endoscopy revealed resolution of the hemangiomas, and the patient subsequently tolerated a lower dose of dasatinib. The other observed DLTs included hypoalbuminemia secondary to proteinuria, diarrhea (two patients), grade 2 rash (with the patient electing to discontinue treatment), and hypokalemia.

Clinical Activity

No complete or partial objective responses were observed in patients with solid tumors. Two patients treated at 110 mg/m²/dose had prolonged stable disease (an 11-year-old girl with neuroblastoma who received five cycles of protocol therapy and a 15-year-old girl with neuroendocrine carcinoma who received nine cycles of protocol therapy). Both patients were removed from protocol therapy for toxicity rather than disease progression. None of the five patients with osteosarcoma experienced disease stabilization beyond the first course of therapy.

The first patient with Ph-positive ALL experienced disease progression during the first course of treatment. The second patient had a hypoplastic bone marrow at the end of course 1 and was taken off study after course 2 for dasatinib-associated diarrhea. Bone marrow evaluation was not performed at the end of course 2. Best response data for patients with CML are listed in Table 4. All nine evaluable patients had a response to therapy, although only two patients experienced reduction in bone marrow blasts and a minor or minimal

Toxicity

In the solid tumor stratum, the MTD was 85 mg/m²/dose, with two of six patients treated at 110 mg/m²/dose developing DLTs (Table 2); a 20-year-old woman with a leiomyosarcoma developed grade 2

Table 3. DLTs After Course 1

Patient No.	Stratum	Dose Level (mg/m ²)	Course No.	Toxicity	Toxicity Grade
10	Leukemia	50	2	Hypoalbuminemia	2
10	Leukemia	50	3	Proteinuria	3
17	Leukemia	65	5	Hemorrhage, GI/colon	3
17	Leukemia	65	5	Vascular, other (hemangiomatosis)	3
27	Leukemia	85	2	Diarrhea	3
39	Leukemia	85	5	Diarrhea	3
21	Solid tumor	110	4	Pleural effusion (nonmalignant)	2
21	Solid tumor	110	5	Pleural effusion (nonmalignant)	2
23	Solid tumor	110	2	Pain chest/thorax NOS	3
23	Solid tumor	110	2	Pleural effusion (nonmalignant)	2
31	Solid tumor	110	3	Rash/desquamation	3
31	Solid tumor	110	9	Rash/desquamation	3

Abbreviations: DLT, dose-limiting toxicity; NOS, not otherwise specified.

cytogenetic response. The median number of courses was three (range, one to 20 courses), and the median time to best response was three cycles (range, one to three cycles) for patients who achieved a cytogenetic CR. Five patients with CML received stem-cell transplantation after dasatinib therapy. Two patients who went off study for unacceptable toxicity were treated at lower doses of dasatinib, and two patients did not have subsequent treatment data available.

Pharmacokinetics

Dasatinib pharmacokinetic parameters after single-dose administration to 19 pediatric patients are listed in Table 5. Dasatinib was rapidly absorbed, with a median T_{max} of 1.0 hours (range, 0.28 to 6.3 hours). Wide interpatient variability in half-life, AUC, and clearance was observed. The median terminal elimination half-life was 2.3 hours (range, 1.7 to 5.3 hours). $AUC_{0-\infty}$ was generally dose proportional. One metabolite contributing less than 10% of overall drug exposure was also observed (data not shown).

DISCUSSION

In pediatric patients with refractory solid tumors, the MTD of dasatinib was 85 mg/m²/dose administered twice daily. Overall, dasatinib was well tolerated, with headache and rash proving to be dose limiting. Pleural effusions, also seen in adult dasatinib trials, were observed in two patients who received multiple courses of dasatinib therapy. The

other observed adverse effects were similar in distribution, frequency, and intensity with those seen in adults, with the notable exception of a single case of hemangiomatosis.⁴⁻⁷ Although the attribution of hemangiomatosis to dasatinib treatment is unclear, we could not exclude a possible drug relationship, especially with respect to bleeding from a previously undiagnosed lesion. All observed toxicities resolved without sequelae after discontinuation of dasatinib therapy.

The pediatric MTD of 85 mg/m²/dose is higher than the approved adult doses of 100 mg (approximately 60 mg/m²) daily for patients with chronic-phase (CP) CML or 140 mg (approximately 80 mg/m²/dose) administered daily for patients with advanced-phase CML or Ph-positive ALL.¹¹ Dasatinib exposure seemed proportional to dose administered. The C_{max} and AUCs in pediatric patients were similar to the C_{max} and AUC observed in an adult pharmacokinetic study (C_{max} , 104.5 ng/mL; coefficient of variation, 29%; $AUC_{0-\infty}$, 313.9 ng · h/mL; coefficient of variation, 42%).¹²

We opted not to attempt to define a separate MTD in patients with leukemia, in part because of the limited number of such patients potentially eligible for phase I investigation in the imatinib era. In an effort to gain initial experience with dasatinib in children with leukemia, the trial was designed to allow for accrual to the leukemia stratum, which lagged one dose level below the solid tumor stratum. One patient developed grade 4 hypokalemia at the 50 mg/m²/dose level but was clinically managed, and dose escalation was allowed for other patients. Similar to adult patients, the majority of children with CML

Table 4. Leukemia Response Data for Patients With CML

Patient No.	Dose Level (mg/m ²)	Prior SCT	Disease Status at Study Entry	Best Response	No. of Courses to Best Response	Total No. of Courses
3	50	No	—	Not evaluable	NA	2
10	50	No	Cytogenetic relapse	Cytogenetic CR	3	3
17	65	Yes	Cytogenetic relapse	Cytogenetic CR	3	22
20	65	No	Cytogenetic relapse	Cytogenetic PR	1	2
24	85	No	Cytogenetic relapse	Cytogenetic PR	1	2
25	85	No	Hematologic relapse	Hematologic CR and cytogenetic PR	1	3
37	85	No	Cytogenetic relapse	Cytogenetic CR	3	9
39	85	No	Cytogenetic relapse	Minimal cytogenetic response	1	6
40	85	No	Cytogenetic relapse	Minor cytogenetic response	1	1

Abbreviations: CML, chronic myeloid leukemia; SCT, stem-cell transplantation; NA, not applicable; CR, complete response; PR, partial response.

Table 5. Dasatinib Pharmacokinetic Data

Dose and Patient No.	Age (years)	BSA (m ²)	C _{max} (ng/mL)	T _{max} (hours)	t _{last} (hours)	AUC _{0-last} (ng · h/mL)	AUC _{0-∞} (ng · h/mL)	t _{1/2} (hours)	CL/F (mL/min/m ²)
50 mg/m²									
2	14	1.7	55	1.50	9.0	235	274	3.1	5,175
4	8	1.07	36	4.00	9.0	176	198	2.8	4,631
6	16	1.47	161	0.55	9.1	327	339	2.0	3,687
10	10	0.99	56	0.60	9.0	204	224	2.4	3,725
Mean			77	1.66		236	259	2.6	4,304
SD			57	1.62		66	62	0.4	726
Median			55	1.05		220	249	2.6	4,178
65 mg/m²									
9	16	1.79	244	1.00	6.6	476	608	4.3	3,153
17	2	0.56	165	0.50	9.0	301	315	2.3	1,851
8	9	1.21	134	2.00	9.0	404	421	2.0	3,165
13	7	0.78	77	0.50	9.0	200	206	2.2	4,044
Mean			155	1.00		345	388	2.7	3,053
SD			70	0.71		121	171	1.1	903
Median			149	0.75		353	368	2.2	3,159
85 mg/m²									
15	17	1.7	142	0.50	8.8	323	351	2.5	6,881
37	13	2.1	155	1.00	9.1	730	779	1.8	3,742
18	5	2.0	81	2.00	9.0	391	415	1.7	6,831
28	14	1.33	242	4.03	9.9	923	982	1.8	1,952
16	2	0.54	125	1.00	9.0	301	317	2.3	2,369
36	7	0.87	133	2.05	9.1	577	596	1.6	2,096
Mean			146	1.76		541	573	1.9	3,979
SD			53	1.27		249	265	0.3	2,318
Median			137	1.50		484	506	1.8	3,056
110 mg/m²									
30	20	1.85	151	0.50	9.0	364	396	2.7	8,410
29	14	1.67	134	2.00	9.1	759	1,163	5.3	2,650
22	11	2.0	263	6.27	9.3	540	605	4.0	6,064
23	14	1.4	450	0.28	9.0	770	805	2.2	3,209
Mean			250	2.26		608	742	3.6	5,083
SD			146	2.78		194	326	1.4	2,674
Median			207	1.25		649	705	3.4	4,637

NOTE. Includes data only up to 9-hour time point because of sparse data.

Abbreviations: BSA, body-surface area; C_{max}, peak concentration; T_{max}, time to peak concentration; t_{last}, last time point; AUC_{0-last}, area under the concentration curve to the last measured time point; AUC_{0-∞}, area under the concentration curve extrapolated to infinity; t_{1/2}, terminal half-life; CL/F, apparent clearance; SD, standard deviation.

achieved a cytogenetic CR. However, because most patients with CML proceeded to stem-cell transplantation, we were not able to estimate the duration of response.

On the basis of these results, a phase II trial in patients with select solid tumors is under consideration. A pediatric phase II trial of dasatinib for de novo CP-CML, imatinib-resistant CP-CML, advanced-phase CML, blast-phase CML, and Ph-positive ALL will use a dose of 60 mg/m² daily for CP-CML and 80 mg/m² daily for other leukemia strata. Additionally, Children's Oncology Group study AALL0662 is evaluating dasatinib 60 mg/m² daily in combination with standard chemotherapy for patients with newly diagnosed Ph-positive ALL. Data from this phase I trial suggest that higher doses of dasatinib could be explored if necessary.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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