ORIGINAL ARTICLE

Dasatinib versus Imatinib in Newly Diagnosed Chronic-Phase Chronic Myeloid Leukemia

Hagop Kantarjian, M.D., Neil P. Shah, M.D., Ph.D., Andreas Hochhaus, M.D., Jorge Cortes, M.D., Sandip Shah, M.D., Manuel Ayala, M.D., Beatriz Moiraghi, M.D., Zhixiang Shen, M.D., Jiri Mayer, M.D., Ricardo Pasquini, M.D., Hirohisa Nakamae, M.D., Ph.D., Françoise Huguet, M.D., Concepción Boqué, M.D., Charles Chuah, M.R.C.P., M.D., Eric Bleickardt, M.D., M. Brigid Bradley-Garelik, M.D., Chao Zhu, Ph.D., Ted Szatrowski, M.D., David Shapiro, M.D., and Michele Baccarani, M.D.

From the University of Texas M.D. Anderson Cancer Center, Houston (H.K., J.C.); University of California San Francisco School of Medicine, San Francisco (N.P.S.); the Department of Hematology and Oncology, Universitätsklinikum Jena, Jena, Germany (A.H.); Hemato-Oncology Clinic, Vedanta, Ahmedabad, India (S.S.); Hospital de Especialidades CMN "La Raza," Instituto Mexicano del Seguro Social, Mexico City (M.A.); Hospital General de Agudos J.M. Ramos Mejia, Buenos Aires (B.M.); Rui Jin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai (Z.S.); Interni Hematoonkologicka Klinika, University Hospital Brno, Brno, Czech Republic (J.M.); Hospital de Clínicas de Curitiba, Parana, Brazil (R.P.); Graduate School of Medicine, Osaka City University, Osaka, Japan (H.N.); the Department of Hematology, Hôpital Purpan, Toulouse, France (F.H.); the Department of Clinical Hematology, Institut Català d'Oncologia, Hospitalet de Llobregat, Barcelona (C.B.); Singapore General Hospital, Duke-NUS Graduate Medical School, Singapore (C.C.); Bristol-Myers Squibb, Wallingford, CT (E.B., M.B.B.-G., C.Z., D.S.); Bristol-Myers Squibb, Princeton, NJ (T.S.); and the Department of Hematology–Oncology "L. and A. Seràgnoli," University of Bologna, Bologna, Italy (M.B.). Address reprint requests to Dr. Kantarjian at the Department of Leukemia, University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030, or at hkantarj@mdanderson.org.

Drs. Kantarjian and Shah contributed equally to this article.

Investigators who participated in the Dasatinib versus Imatinib Study in Treatment-Naive CML Patients (DASISION) are listed in the Appendix.

This article (10.1056/NEJMoa1002315) was published on June 5, 2010, at NEJM.org.

N Engl J Med 2010;362:2260-70.

ABSTRACT

BACKGROUND

Treatment with dasatinib, a highly potent BCR-ABL kinase inhibitor, has resulted in high rates of complete cytogenetic response and progression-free survival among patients with chronic myeloid leukemia (CML) in the chronic phase, after failure of imatinib treatment. We assessed the efficacy and safety of dasatinib, as compared with imatinib, for the first-line treatment of chronic-phase CML.

METHODS

In a multinational study, 519 patients with newly diagnosed chronic-phase CML were randomly assigned to receive dasatinib at a dose of 100 mg once daily (259 patients) or imatinib at a dose of 400 mg once daily (260 patients). The primary end point was complete cytogenetic response by 12 months, confirmed on two consecutive assessments at least 28 days apart. Secondary end points, including major molecular response, were tested at a significance level of 0.0001 to adjust for multiple comparisons.

RESULTS

After a minimum follow-up of 12 months, the rate of confirmed complete cytogenetic response was higher with dasatinib than with imatinib (77% vs. 66%, $P=0.007$), as was the rate of complete cytogenetic response observed on at least one assessment (83% vs. 72%, $P=0.001$). The rate of major molecular response was higher with dasatinib than with imatinib (46% vs. 28%, $P<0.0001$), and responses were achieved in a shorter time with dasatinib ($P<0.0001$). Progression to the accelerated or blastic phase of CML occurred in 5 patients who were receiving dasatinib (1.9%) and in 9 patients who were receiving imatinib (3.5%). The safety profiles of the two treatments were similar.

CONCLUSIONS

Dasatinib, administered once daily, as compared with imatinib, administered once daily, induced significantly higher and faster rates of complete cytogenetic response and major molecular response. Since achieving complete cytogenetic response within 12 months has been associated with better long-term, progression-free survival, dasatinib may improve the long-term outcomes among patients with newly diagnosed chronic-phase CML. (ClinicalTrials.gov number, NCT00481247.)

Chronic myeloid leukemia (CML) in the chronic phase, a clonal myeloproliferative disorder, is caused by the constitutively active BCR-ABL tyrosine kinase resulting from the translocation that produces the Philadelphia (Ph) chromosome.[1,2] Imatinib (Gleevec, Novartis Pharmaceuticals), an inhibitor of the BCR-ABL kinase, is the standard first-line therapy for patients with chronic-phase CML.[3-6] Dasatinib (Sprycel, Bristol-Myers Squibb), a second-generation BCR-ABL kinase inhibitor, has been approved as a second-line treatment for patients with CML if imatinib therapy fails.[4-7] Dasatinib therapy induces a complete cytogenetic response in approximately 50% of patients who do not have a response to imatinib or cannot tolerate it.[8-10]

Among patients with newly diagnosed chronic-phase CML who are receiving imatinib, the long-term outcome is more favorable for those in whom a complete cytogenetic response is achieved at 12 months or earlier than for those in whom a complete cytogenetic response is not achieved by 12 months.[6,11-16] In the pivotal study of imatinib, 97% of patients in whom a complete cytogenetic response had been achieved at 12 months, as compared with 81% of patients who did not have a major cytogenetic response at 12 months, were free from progression to the accelerated or blastic phase of CML at 5 years[11] — a risk of disease progression that was lower by a factor of six. A similar correlation has been shown between complete cytogenetic response at 6 months and freedom from progression to the accelerated or blastic phase at 6 years.[13] Since 30 to 40% of patients who receive imatinib do not have a complete cytogenetic response by 12 months,[11,12] it is hypothesized that initial therapy with more potent tyrosine kinase inhibitors that may improve the rate of complete cytogenetic response early after diagnosis could improve the long-term outcome in patients with CML.

Dasatinib is 325 times as potent as imatinib in inhibiting unmutated BCR-ABL kinase in vitro.[17] Since increased inhibition of BCR-ABL kinase correlates with a better clinical response,[18] administration of dasatinib as the initial therapy may improve responses in patients with newly diagnosed chronic-phase CML. In an exploratory, single-institution, phase 2 study involving patients with newly diagnosed chronic-phase CML, dasatinib induced a complete cytogenetic response by 12 months in 98% of the patients and had an acceptable side-effect profile.[19] Because dasatinib is less vulnerable to resistance-conferring mutations in the BCR-ABL kinase domain than is imatinib,[20-22] the incidence of disease progression may be reduced among patients treated with dasatinib. The Dasatinib versus Imatinib Study in Treatment-Naive CML Patients (DASISION) was undertaken to compare the efficacy and safety of dasatinib, administered at a dose of 100 mg once daily, with those of imatinib, administered at a dose of 400 mg once daily, among patients with newly diagnosed chronic-phase CML. The primary objective of the study was to determine whether patients who received dasatinib had a higher rate of confirmed complete cytogenetic response by 12 months after the initiation of treatment.

Methods

Study Oversight

The study protocol was reviewed by the ethics committee or institutional review board at each participating center. All patients gave written informed consent. The study was designed by the investigators and representatives of the sponsor, Bristol-Myers Squibb. Data were collected with the use of the data management system of Bristol-Myers Squibb. The study steering committee (see the Appendix), whose members also served as the writing committee, and authors from Bristol-Myers Squibb analyzed and interpreted the data, wrote the manuscript, and take responsibility for the accuracy and completeness of the data. With the use of a manuscript outline developed with intellectual input and supervision from the writing committee throughout, a representative from Bristol-Myers Squibb prepared the first draft of the manuscript. The decision to submit the manuscript for publication was made jointly by the sponsor and the study steering committee, after unblinding of the data. The protocol (as amended), including the statistical analysis plan, is available with the full text of this article at NEJM.org. All authors vouch for the accuracy and completeness of the reported data; all attest that this report is in concordance with the study protocol.

Patients

Adults in whom Ph-positive, chronic-phase CML had been diagnosed by means of bone marrow cytogenetic studies performed within 3 months before study entry were eligible for inclusion in the study. Chronic-phase CML was defined by the

presence of less than 15% blasts, less than 20% basophils, and less than 30% blasts plus promyelocytes in the peripheral blood and bone marrow and a platelet count of 100×10^9 per liter or more, with an absence of extramedullary disease except for hepatosplenomegaly.[5] Eligible patients must have received no previous treatment for CML except for anagrelide or hydroxyurea and had to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 and adequate hepatic and renal function. ECOG performance status is scored on a scale of 0 to 5, with 0 indicating that the patient is fully active and able to carry on all predisease activities without restriction; 1 indicating that the patient is restricted in physically strenuous activity but is ambulatory and able to carry out work of a light or sedentary nature, such as light housework or office

Table 1. Demographic Characteristics of the Patients and Baseline Disease Characteristics.

Characteristic	Dasatinib (N=259)	Imatinib (N=260)
Age		
Median — yr	46	49
Range — yr	18–84	18–78
>65 yr — no. (%)	20 (8)	24 (9)
Sex — no. (%)		
Male	144 (56)	163 (63)
Female	115 (44)	97 (37)
ECOG performance status — no. (%)*		
0	213 (82)	205 (79)
1	46 (18)	53 (20)
2	0	2 (1)
Hasford risk — no. (%)†		
Low	86 (33)	87 (33)
Intermediate	124 (48)	123 (47)
High	49 (19)	50 (19)
Time from diagnosis to randomization — mo		
Median	1	1
Range	0.03–9.7	0.1–8.0
White-cell count — $\times10^{-9}$/liter		
Median	25.1	23.5
Range	2.5–493.0	1.4–475.0
Platelet count — $\times10^{-9}$/liter		
Median	448	390
Range	58–1880	29–2930
Peripheral-blood blasts — %		
Median	1.0	1.0
Range	0.0–10.0	0.0–11.0
Peripheral-blood basophils — %		
Median	4.0	4.0
Range	0.0–27.8‡	0.0–19.5
Bone marrow blasts — %		
Median	2.0	2.0
Range	0.0–14.0	0.0–12.0

Table 1. (Continued.)

Characteristic	Dasatinib (N=259)	Imatinib (N=260)
BCR-ABL transcript type — no. (%)	258 (100)	258 (99)
b2a2 and b3a2	253 (98)	255 (98)
b2a3	1 (<1)	1 (<1)
b3a3	1 (<1)	1 (<1)
Rare variant	3 (1)	1 (<1)
Previous therapy for CML — no. (%)		
Hydroxyurea	189 (73)	190 (73)
Anagrelide	8 (3)	3 (1)
Imatinib	3 (1)	4 (2)

* Eastern Cooperative Oncology Group (ECOG) performance status is graded on a scale of 0 to 5, with 0 indicating that the patient is fully active and able to carry on all predisease activities without restriction and 5 indicating that the patient has died.

† The Hasford risk score is calculated with the use of the following equation: (0.6666 × age score [0 for <50 years, 1 for older age] + 0.0420 × spleen size [cm below costal margin] + 0.0584 × blasts [%] + 0.0413 × eosinophils [%] + 0.2039 × basophil score [0 for <3%, 1 for higher value] + 1.0956 × platelet score [0 for $<1500\times10^9$ per liter; 1 for a higher value]) × 1000. A score of less than 780 is considered to indicate low risk, a score of 780 to 1480, intermediate risk, and a score higher than 1480, high risk.

‡ Two patients with basophil counts of 26% and 28% at baseline had basophil counts of 19% and 16%, respectively, at screening and were eligible.

work; and 2 indicating that the patient is ambulatory and capable of all self-care but is unable to carry out any work activities; a score of 5 indicates death.[23] Adequate hepatic and renal function was defined as a maximum total bilirubin level of 2 times the upper limit of the normal range, maximum levels of aspartate aminotransferase and alanine aminotransferase of 2.5 times the upper limit of the normal range, and a maximum serum creatinine level of 3 times the upper limit of the normal range. Women who were breast-feeding, were pregnant, or could potentially become pregnant and did not have documentation of a negative pregnancy test were excluded. Other key exclusion criteria were serious, uncontrolled medical disorders or active infections; uncontrolled or serious cardiovascular disease; a corrected QT (QTc) interval of more than 450 msec; a history of a serious bleeding disorder unrelated to CML; previous or concurrent cancer (other than basal-cell skin cancer); previous chemotherapy for peripheral stem-cell mobilization; and pleural effusion at baseline.

STUDY DESIGN AND TREATMENT

DASISION was an open-label, multinational, randomized phase 3 trial. Patients were stratified according to the Hasford risk score.[24] The score is calculated with the use of the following equation: (0.6666 × age [0 for <50 years; 1 for older age] + 0.0420 × spleen size [cm below costal margin] + 0.0584 × blasts [%] + 0.0413 × eosinophils [%] + 0.2039 × basophils [0 for <3%; 1 for higher value] + 1.0956 × platelet count [0 for $<1500\times10^9$ per liter; 1 for a higher value]) × 1000. A score of less than 780 is considered to indicate low risk, a score of 780 to 1480, intermediate risk, and a score higher than 1480, high risk. Patients were randomly assigned, in a 1:1 ratio, to receive either dasatinib, administered orally at a dose of 100 mg once daily (with or without food), or imatinib, administered orally at a dose of 400 mg once daily (with food). Patients continued to receive the study treatment until the disease progressed or unacceptable toxic effects developed. Interruptions of therapy or dose reductions or escalations were allowed in the case of both treatments. Criteria for these dose modifications are detailed in Table 1 in the Supplementary Appendix, available at NEJM.org.

EVALUATION OF EFFICACY

A complete cytogenetic response, defined as the absence of Ph-positive metaphases, was determined on the basis of G-banding in at least 20 cells in metaphase per bone marrow sample.

Samples were collected within 6 weeks after randomization and every 3 months thereafter. If a sample had fewer than 20 cells in metaphase, the assessment was repeated within 4 weeks. A confirmed complete cytogenetic response by 12 months after the initiation of treatment was the primary end point. A confirmed complete cytogenetic response was defined as a complete cytogenetic response documented on two consecutive assessments at least 28 days apart. Patients who had a first assessment of complete cytogenetic response at 12 months that was confirmed on a second assessment thereafter were considered to have had a confirmed complete cytogenetic response by 12 months.

A major molecular response at any time, the time to a confirmed complete cytogenetic response, and the time to a major molecular response were secondary end points. Other end points were the rates of complete cytogenetic response (observed at least once in at least 20 metaphases) and of major molecular response by 12 months, progression-free survival, and overall survival. Achievement of a major molecular response was assessed with the use of a quantitative reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay at a centralized laboratory (MolecularMD, Portland, OR). Total RNA was extracted from peripheral-blood samples (5 to 10 ml) collected in PAXgene reagent (Qiagen)[25] at baseline and every 3 months. RNA was analyzed by means of a quantitative RT-PCR assay to quantitate *BCR-ABL* and *ABL* transcripts. A major molecular response was defined as a *BCR-ABL* transcript level of 0.1% or lower on the International Scale (conversion factor of 0.81), corresponding to a reduction in the *BCR-ABL* transcript level by at least 3 log from the standardized baseline level.[26]

The disease was considered to have progressed if any of the following occurred: a doubling of the white-cell count to more than 20×10^9 per liter in the absence of complete hematologic response; a loss of complete hematologic response; an increase in Ph-positive bone marrow metaphases to more than 35%; progression to accelerated-phase or blastic-phase CML; or death from any cause.[5]

EVALUATION OF SAFETY

Adverse events were assessed continuously for all treated patients and were graded according to the Common Terminology Criteria for Adverse Events, version 3.0, of the National Cancer Institute (http://ctep.info.nih.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf). Since pleural effusion is seen in patients with CML who are treated with dasatinib,[19,27] a chest radiograph to check for the presence of pleural effusion was obtained in all patients, per protocol, at baseline and at 6 months of treatment or more frequently, if indicated clinically.

STATISTICAL ANALYSIS

All the efficacy analyses were performed on the basis of the intention-to-treat principle. The primary end point was tested at a significance level of 0.05 with the use of the Cochran–Mantel–Haenszel test, with adjustment for stratification according to the Hasford score. Differences in the rate of a major molecular response at any time, the time to a confirmed complete cytogenetic response, and the time to a major molecular response were tested at a significance level of 0.0001. Other comparisons were post hoc analyses. Associated P values for post hoc analyses have not been adjusted for multiple comparisons and are provided for descriptive purposes. The times to a complete cytogenetic response and to a major molecular response were calculated with the use of the Kaplan–Meier product-limit method. Differences between the treatment groups in times to an event were evaluated with the use of a stratified log-rank test. Response rates were binomial, and their 95% confidence intervals were calculated with the use of the Clopper–Pearson method. All reported P values and 95% confidence intervals are two-sided.

RESULTS

PATIENTS AND TREATMENT

A total of 547 patients with newly diagnosed chronic-phase CML were assessed for eligibility between September 2007 and December 2008 at 108 study centers in 26 countries; of these patients, 519 were randomly assigned to receive dasatinib (259 patients) or imatinib (260 patients). The baseline demographic characteristics of the patients, the baseline disease characteristics, and the risk stratification were well balanced between the two treatment groups (Table 1). It should be noted that, for a given patient population, the Hasford categorization places fewer patients in the high-risk group[28] than does the categoriza-

tion according to the scoring system devised by Sokal et al.[29]

Of the patients who were randomly assigned to a treatment group, 258 in each group received the study treatment (Table 2). For the present analysis, all patients had a minimum follow-up of 12 months. The median dose of dasatinib that was delivered was 99 mg per day (range, 21 to 136), and the median dose of imatinib delivered was 400 mg per day (range, 125 to 657). The median duration of treatment was 14.0 months (range, 0.03 to 24.1) in the case of dasatinib and 14.3 months (range, 0.3 to 25.8) in the case of imatinib. A total of 84% of the patients receiving dasatinib and 81% of the patients receiving imatinib continued to receive treatment for the duration of the study period reported in this article (Table 2). Treatment is ongoing; the protocol stipulates that an analysis of the efficacy and safety data be performed after a minimum follow-up of 5 years.

Table 2. Treatment Status of Study Patients.*

Treatment Status	Dasatinib	Imatinib
	no. (%)	
Received treatment	258 (100.0)	258 (100.0)
Continue to receive treatment	218 (84.5)	210 (81.4)
Discontinued treatment	40 (15.5)	48 (18.6)
Had drug-related adverse events	13 (5.0)	11 (4.3)
Hematologic, including cytopenia	4 (1.6)	3 (1.2)
Nonhematologic	9 (3.5)	8 (3.1)
Disease progressed†	11 (4.3)	14 (5.4)
Increased white-cell count	1 (0.4)	0
Loss of complete hematologic response	0	0
Loss of major cytogenetic response	1 (0.4)	4 (1.6)
Progression to accelerated or blastic phase	5 (1.9)	9 (3.5)
Death	4 (1.6)	1 (0.4)
Treatment failed†	6 (2.3)	10 (3.9)
Did not have complete hematologic response or cytogenetic response at 6 mo	2 (0.8)	4 (1.6)
Had less than partial cytogenetic response at 12 mo	3 (1.2)	6 (2.3)
Did not have complete cytogenetic response at 18 mo	1 (0.4)	0
Had adverse event unrelated to drug	3 (1.2)	1 (0.4)
Withdrew consent	2 (0.8)	3 (1.2)
Became pregnant	2 (0.8)	0
Did not adhere to therapy	0	2 (0.8)
Was lost to follow-up	0	3 (1.2)
Requested to discontinue‡	2 (0.8)	1 (0.4)
Had other reason	1 (0.4)	3 (1.2)

* Of 547 patients assessed for eligibility, 28 were not randomly assigned to a study treatment: 20 patients no longer met the inclusion criteria, 3 refused to participate, and 5 had other reasons. Data for all 519 patients who were randomly assigned (259 in the dasatinib group and 260 in the imatinib group) were included in the analysis of efficacy, and data for 258 in the dasatinib group and 258 in the imatinib group were included in the analysis of safety reported in this table.

† Progression and treatment failure were defined according to the recommendations from European LeukemiaNet.[5]

‡ Included in this category are patients who discontinued treatment but agreed to long-term follow-up.

EFFICACY

The rate of a confirmed complete cytogenetic response by 12 months was significantly higher among patients receiving dasatinib than among patients receiving imatinib (77% vs. 66%, P=0.007) (Table 3). The rate of a complete cytogenetic response by 12 months observed on at least one assessment was also higher with dasatinib treatment than with imatinib treatment (83% vs. 72%, P=0.001).

The rate of a major molecular response at any time was significantly higher among patients receiving dasatinib than among patients receiving imatinib (52% vs. 34%, P<0.0001) (Table 3). The rate of a major molecular response by 12 months was also higher with dasatinib treatment than with imatinib treatment (46% vs. 28%, P<0.0001). In addition, among patients in whom a complete cytogenetic response was achieved by 12 months, the rate of a major molecular response was higher among patients receiving dasatinib than among patients receiving imatinib (54% vs. 39%, P=0.002).

Responses were achieved more quickly with dasatinib than with imatinib. The rates of complete cytogenetic response by 3, 6, and 9 months after the initiation of dasatinib treatment were 54%, 73%, and 78%, respectively, and the rates after the initiation of imatinib treatment were 31%, 59%, and 67%, respectively (Fig. 1A). The time to a complete cytogenetic response was significantly shorter with dasatinib treatment than with imatinib treatment (hazard ratio for shorter time to response with dasatinib, 1.5; P<0.0001). The time to a confirmed complete cytogenetic response was significantly shorter with dasatinib treatment than with imatinib treatment (hazard ratio for shorter time to response, 1.5; P<0.0001). The rates of a major

Table 3. Response Rates.*

Response	Dasatinib (N=259)		Imatinib (N=260)		P Value
	no.	*% (95% CI)*	*no.*	*% (95% CI)*	
Confirmed complete cytogenetic response by 12 mo	199	77 (71–82)	172	66 (60–72)	0.007†
Complete cytogenetic response by 12 mo	216	83 (78–88)	186	72 (66–77)	0.001‡
Major molecular response at any time	135	52 (46–58)	88	34 (28–40)	<0.0001†
Major molecular response by 12 mo	119	46 (40–52)	73	28 (23–34)	<0.0001‡

* All P values were adjusted for the Hasford score.[24] CI denotes confidence interval.
† This was a prespecified analysis; P values have been adjusted for multiple comparisons.
‡ This was a post hoc analysis; P values have not been adjusted for multiple comparisons.

molecular response by 3, 6, and 9 months after the initiation of dasatinib treatment were 8%, 27%, and 39%, respectively, and the rates after the initiation of imatinib treatment were 0.4%, 8%, and 18%, respectively (Fig. 1B). The time to a major molecular response was also significantly shorter with dasatinib treatment than with imatinib treatment (hazard ratio for shorter time to response, 2.0; P<0.0001).

The rates of response by 12 months were higher among patients receiving dasatinib than among patients receiving imatinib across all Hasford risk categories. The rates of complete cytogenetic response by 12 months in the dasatinib group were 94% among patients with low risk scores, 78% among those with intermediate risk scores, and 78% among those with high risk scores. The corresponding rates in the imatinib group were 76%, 72%, and 64%. The rates of major molecular response by 12 months in the dasatinib group were 56% among patients at low risk, 45% among patients at intermediate risk, and 31% among patients at high risk. The corresponding rates in the imatinib group were 36%, 28%, and 16%.

Progression to the accelerated or blastic phase of CML occurred in 5 of 259 patients who were receiving dasatinib (1.9%, all blastic phase) and in 9 of 260 patients who were receiving imatinib (3.5%, all blastic phase) (Table 2). At 12 months, the estimated rates of progression-free survival were similar for patients who were receiving dasatinib and those who were receiving imatinib (96% and 97%, respectively). None of the patients in whom a major molecular response was achieved have had progression to the accelerated or blastic phase during the current follow-up. At 12 months, the estimated rates of overall survival were 97% among patients receiving dasatinib and 99% among those receiving imatinib.

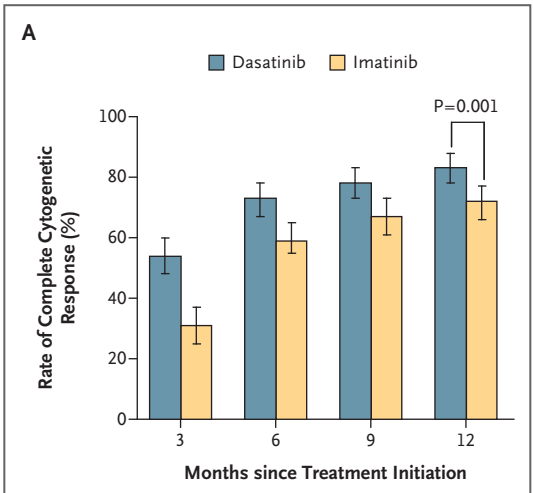
SAFETY

Drug-related adverse events associated with both treatments were primarily grade 1 or grade 2 events (Table 4). Grade 3 or 4 neutropenia occurred with similar frequency among the patients receiving dasatinib and those receiving imatinib (21% and 20%, respectively); the rate of thrombocytopenia was 19% among patients receiving dasatinib, as compared with 10% among those receiving imatinib. Of the nonhematologic adverse drug reactions occurring in at least 10% of the treated patients, most of them — including nausea, vomiting, muscle inflammation, rash, and fluid retention — occurred less frequently among patients receiving dasatinib than among those receiving imatinib (Table 4).

Fluid retention (all grades) occurred more frequently with imatinib than with dasatinib (42% vs. 19%), as did superficial edema (36% vs. 9%). Pleural effusion was reported only in the dasatinib group: 26 patients (10%) had pleural effusion; all events were grade 1 (2%) or grade 2 (8%). All the cases were managed by means of a protocol-stipulated dose-modification schema, medical intervention, or both. Therapy was interrupted in 19 patients, and the dose of the study drug was reduced in 8 patients. Three patients (1.2%) underwent thoracentesis (two for diagnostic purposes and one for therapeutic reasons), 12 received diuretics, and 7 received corticosteroids. A complete cytogenetic response was achieved by 12 months in 24 of the 26 patients with pleural effusion (92%).

Gastrointestinal or other bleeding events occurred in 13 patients receiving dasatinib (5%) and in 12 patients receiving imatinib (5%); in one patient in the dasatinib group and two patients in the imatinib group, the episode was a grade 3 or 4 event. Grade 3 or 4 hypophosphatemia occurred in 4% of the dasatinib-treated patients and in 21% of the imatinib-treated patients. Six patients in the dasatinib group (2%) and 9 in the imatinib group (4%) had QTc intervals between 450 msec and 500 msec. One patient in each group (0.4%) had a QTc interval of greater than 500 msec. The median changes in QTc interval from baseline were 3.0 msec in the dasatinib group and 8.2 msec in the imatinib group.

The overall rates of discontinuation of therapy because of toxic effects of the drug were 5% among patients who were receiving dasatinib and 4% among those who were receiving imatinib (Table 2). Nearly three fourths of the episodes of cytopenia occurred during the first 4 months of treatment in both groups, with only four patients in the dasatinib group and three in the imatinib group discontinuing treatment owing to drug-related cytopenia. Three patients in the dasatinib group discontinued treatment owing to grade 2 pleural effusion. In the imatinib group, two patients discontinued treatment owing to liver-function abnormalities, one patient owing to hypophosphatemia, and one patient owing to hypocalcemia. One patient in the dasatinib group discontinued therapy because of an elevated serum level of creatine phosphokinase; there was no evidence of myocardial ischemia. One death in each group was attributed to the study treatment; both deaths were the result of myocardial infarction.



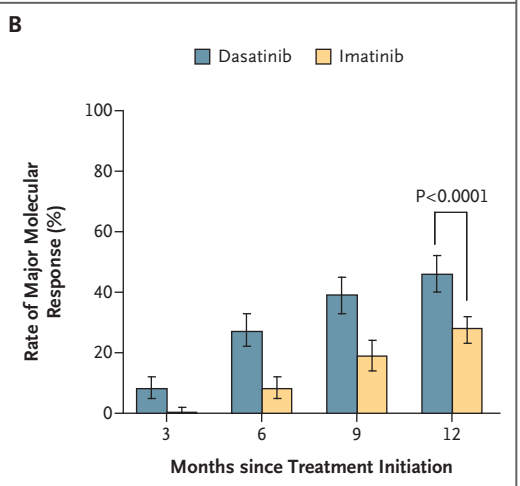


Figure 1. Response Rates over Time.

The rates of complete cytogenetic response are shown in Panel A. A total of 10 patients (5 in each group) in whom the assessment of complete cytogenetic response was based on bone marrow samples containing fewer than 20 cells in metaphase per sample were categorized as not having a response. The rates of major molecular response are shown in Panel B. A total of 8 patients (5 in the dasatinib group and 3 in the imatinib group) with atypical transcripts at baseline were categorized as not having a response. I bars indicate 95% confidence intervals.

DISCUSSION

In this randomized, phase 3 study involving patients with newly diagnosed chronic-phase CML, treatment with dasatinib, administered at a dose of 100 mg once daily, was compared with the current standard first-line therapy, imatinib, administered at a dose of 400 mg once daily. After a minimum follow-up of 12 months and a median duration of treatment of 14 months, the rate of confirmed complete cytogenetic response by 12 months was significantly higher among patients treated with dasatinib than among those treated with imatinib (P=0.007). The rate of major molecular response was also higher with dasatinib than with imatinib (P<0.0001). Responses were achieved significantly faster with dasatinib than with imatinib (P<0.0001). Dasatinib was more effective than imatinib across all Hasford risk groups. Collectively, these results suggest that dasatinib has greater potency than imatinib against the BCR-ABL kinase[17,20,21] and show that

Table 4. Drug-Related Adverse Events That Occurred in at Least 10% of Treated Patients.

Event	Dasatinib (N=258)		Imatinib (N=258)	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
	% of patients			
Cytopenia				
Neutropenia	65	21	58	20
Thrombocytopenia	70	19	62	10
Anemia	90	10	84	7
Nonhematologic adverse event				
Fluid retention	19	1	42	1
Superficial edema	9	0	36	<1
Pleural effusion	10	0	0	0
Other	5	1	8	<1
Diarrhea	17	<1	17	1
Nausea	8	0	20	0
Vomiting	5	0	10	0
Myalgia	6	0	12	0
Muscle inflammation	4	0	17	<1
Musculoskeletal pain	11	0	14	<1
Rash	11	0	17	1
Headache	12	0	10	0
Fatigue	8	<1	10	0

dasatinib has an efficacy profile that is superior to that of imatinib among patients with newly diagnosed chronic-phase CML. In a recent phase 3 trial (reported elsewhere in this issue of the *Journal*) involving a similar patient population, another second-generation BCR-ABL kinase inhibitor, nilotinib (administered at a dose of 300 mg twice daily or 400 mg twice daily), as compared with imatinib, was associated with an increased rate of major molecular response.[30]

Achievement of both a complete cytogenetic response and a major molecular response within 12 months after the initiation of therapy for newly diagnosed chronic-phase CML is associated with a very low risk of long-term progression.[6,11-16] Achievement of a major molecular response is also correlated with a prolonged complete cytogenetic response.[31-34] None of the patients in whom there was a major molecular response at 12 months after the initiation of imatinib therapy had progression to the accelerated or blastic phase of CML at 8 years.[16] Thus, with longer-term follow-up, it is becoming evident that achieving both a complete cytogenetic response and a major molecular response more quickly and at high rates is an important treatment goal.[13,14] Although the follow-up period in the present study has not been long enough to permit meaningful detection of differences in survival between the treatment groups, the higher rates of complete cytogenetic response and major molecular response with dasatinib, and early evidence of reduced rates of progression to more aggressive phases of CML, suggest that dasatinib treatment may significantly improve the long-term outcome in patients with chronic-phase CML. It is anticipated that the planned 5-year follow-up of patients in this and other studies will answer this question.

Grade 3 or 4 nonhematologic adverse events occurred infrequently in both treatment groups. The rates of discontinuation of therapy owing to drug-related adverse reactions, including cytopenia, were similar. Several nonhematologic adverse events were more common with imatinib than with dasatinib (e.g., fluid retention, which occurred in 19% of the patients in the dasatinib group and in 42% of those in the imatinib group). Episodes of pleural effusion, which were reported in 10% of dasatinib-treated patients, were all grade 1 or 2 and were managed by means of temporary dose reductions, interruptions of therapy, or both. Overall, the safety profile of dasatinib in our study population compares favorably to that reported previously among patients with chronic-phase CML who did not have a response to imatinib or could not tolerate it.[9,10]

In our trial, dasatinib, as compared with imatinib (which is the current standard of care), was associated with significantly higher and faster rates of complete cytogenetic response and major molecular response. Given the established association between a complete cytogenetic response within the first 12 months after the initiation of imatinib therapy and superior long-term progression-free survival, longer follow-up may show that dasatinib therapy improves the long-term outcomes in patients with newly diagnosed chronic-phase CML.

Supported by Bristol-Myers Squibb. Dr. Shah is a Clinical Scholar of the Leukemia and Lymphoma Society.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the patients and investigators for their participation in the trial, Maria Grasic of Bristol-Myers Squibb for protocol management support, and Motasim Billah, also of Bristol-Myers Squibb, for preparation of the first draft of the manuscript.

APPENDIX

Investigators who participated in the DASISION Trial are as follows: **Argentina** — E. Bullorsky, J. Milone, B. Moiraghi, S. Pavlovsky; **Austria** — G. Gastl, P. Valent; **Australia** — S. Durrant, R. Herrmann, A. Nicol, P. Rowlings; **Belgium** — J. Van Droogenbroeck, A. Ferrant; **Brazil** — A. Moellmann Coelho, V. Colturato, P.E. Dorlhiac Llacer, R. Pasquini, C. De Souza, M.A. Zanichelli; **Chile** — M.S. Undurraga; **China** — J. Hu, X. Huang, Z. Shen, J. Wang; **Colombia** — L. Enciso, C. Ramirez; **Czech Republic** — E. Faber, H. Klamova, J. Mayer, J. Voglova; **Denmark** — J. Stentoft; **France** — C. Berthou, D. Bordessoule, A. Buzyn, V. Dubruille, M. Escoffre-Barbe, T. Facon, A. Guerci-Bresler, F. Guilhot-Gaudeffroy, R. Herbrecht, F. Huguet, M. Michallet, D. Rea, J.-F. Rossi; **Germany** — P. Le Coutre, C. Junghanss, M. Soekler, F. Stegelmann; **Greece** — A. Fassas; **Hungary** — S. Fekete, M. Udvardy; **India** — U. Agarwal, V.P. Gangadharan, V. Mathew, G. Narayan, K. Prabhash, T. Saikia, S. Shah; **Italy** — E. Abruzzese, G. Alimena, C. Gambacorti-Passerini, M. Lazzarino, F. Di Raimondo, G. Saglio; **Japan** — H. Akiyama, S. Fujisawa, M. Hino, Y. Ishida, K. Ishizawa, K. Matsue, H. Nakamae, M. Ogura, K. Tamura, M. Tanimoto, M. Taniwaki, K. Usuki, A. Utsunomiya; **Mexico** — D.G. Almaguer, J.L. Ayala, A.A. Gonzalez, J.J. Kassack Ipiña, R.R. Llamas; **the Netherlands** — A.V.M.B. Schattenberg, E. Vellenga; **Peru** — L. Casanova, J. Navarro, J.M. Zenteno; **Poland** — J. Holowiecki, M. Komarnicki, T. Robak, A. Skotnicki, K. Warzocha; **Russia** — N. Khoroshko, Y. Shatokhin, A. Zaritsky; **Singapore** — C.T.H. Chuah; **South Korea** — D.-W. Kim, K.-H. Lee; **Spain** — A. Alvarez, C. Boqué, C. Del Canizo, F. Cervantes, A. Jimenez-Velasco, J. Martinez-Dominguez, A.R. Payer, R. De Paz, M. Perez, J.L. Steegmann; **Turkey** — M. Cetin, I.C. Haznedaroglu. **Study Steering and Writing Committee:** M. Baccarani, J. Cortes, A. Hochhaus, H. Kantarjian, N. Shah.

REFERENCES

1. Faderl S, Talpaz M, Estrov Z, O'Brien S, Kurzrock R, Kantarjian HM. The biology of chronic myeloid leukemia. N Engl J Med 1999;341:164-72.

2. Lugo TG, Pendergast AM, Muller AJ, Witte ON. Tyrosine kinase activity and transformation potency of bcr-abl oncogene products. Science 1990;247:1079-82.

3. Gleevec (imatinib mesylate) tablets: prescribing information. Rev. ed. East Hanover, NJ: Novartis Pharmaceuticals, November 2007.

4. The chronic myelogenous leukemia clinical practice guidelines in oncology, version 1. Washington, DC: National Comprehensive Cancer Network, 2009.

5. Baccarani M, Saglio G, Goldman J, et al. Evolving concepts in the management of chronic myeloid leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet. Blood 2006; 108:1809-20.

6. Baccarani M, Cortes J, Pane F, et al. Chronic myeloid leukemia: an update of concepts and management recommendations of European LeukemiaNet. J Clin Oncol 2009;27:6041-51.

7. Sprycel (dasatinib): prescribing information. Rev. ed. New York: Bristol-Myers Squibb, November 2007.

8. Hochhaus A, Baccarani M, Deininger M, et al. Dasatinib induces durable cytogenetic responses in patients with chronic myelogenous leukemia in chronic phase with resistance or intolerance to imatinib. Leukemia 2008;22:1200-6.

9. Shah NP, Kantarjian HM, Kim DW, et al. Intermittent target inhibition with dasatinib 100 mg once daily preserves efficacy and improves tolerability in imatinib-resistant and -intolerant chronic-phase chronic myeloid leukemia. J Clin Oncol 2008;26:3204-12.

10. Shah NP, Kim D-W, Kantarjian HM, et al. Potent, transient inhibition of BCR-ABL with dasatinib 100 mg daily achieves rapid and durable cytogenetic responses and high transformation-free survival rates in chronic phase chronic myeloid leukemia patients with resistance, suboptimal response or intolerance to imatinib. Haematologica 2010;95:232-40.

11. Druker BJ, Guilhot F, O'Brien SG, et al. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. N Engl J Med 2006;355:2408-17.

12. de Lavallade H, Apperley JF, Khorashad JS, et al. Imatinib for newly diagnosed patients with chronic myeloid leukemia: incidence of sustained responses in an intention-to-treat analysis. J Clin Oncol 2008;26:3358-63.

13. Hochhaus A, O'Brien SG, Guilhot F, et al. Six-year follow-up of patients receiving imatinib for the first-line treatment of chronic myeloid leukemia. Leukemia 2009; 23:1054-61.

14. Quintás-Cardama A, Kantarjian H, Jones D, et al. Delayed achievement of cytogenetic and molecular response is associated with increased risk of progression among patients with chronic myeloid leukemia in early chronic phase receiving high-dose or standard-dose imatinib therapy. Blood 2009;113:6315-21.

15. Roy L, Guilhot J, Krahnke T, et al. Survival advantage from imatinib compared with the combination interferon-alpha plus cytarabine in chronic-phase chronic myelogenous leukemia: historical comparison between two phase 3 trials. Blood 2006;108:1478-84.

16. Deininger M, O'Brien SG, Guilhot F, et al. International Randomized Study of Interferon Vs STI571 (IRIS) 8-year follow up: sustained survival and low risk for progression or events in patients with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP) treated with imatinib. Blood 2009;114:462. abstract.

17. Lombardo LJ, Lee FY, Chen P, et al. Discovery of N-(2-chloro-6-methyl-phenyl)-2-(6-(4-(2-hydroxyethyl)-piperazin-1-yl)-2-methylpyrimidin-4-ylamino)thiazole-5-carboxamide (BMS-354825), a dual Src/Abl kinase inhibitor with potent antitumor activity in preclinical assays. J Med Chem 2004;47:6658-61.

18. White D, Saunders V, Grigg A, et al. Measurement of in vivo BCR-ABL kinase inhibition to monitor imatinib-induced target blockade and predict response in chronic myeloid leukemia. J Clin Oncol 2007;25:4445-51.

19. Cortes JE, Jones D, O'Brien S, et al. Results of dasatinib therapy in patients with early chronic-phase chronic myeloid leukemia. J Clin Oncol 2010;28:398-404.

20. O'Hare T, Walters DK, Stoffregen EP, et al. In vitro activity of Bcr-Abl inhibitors AMN107 and BMS-354825 against clinically relevant imatinib-resistant Abl kinase domain mutants. Cancer Res 2005;65: 4500-5.

21. O'Hare T, Eide CA, Deininger MW. Bcr-Abl kinase domain mutations, drug resistance, and the road to a cure for chronic myeloid leukemia. Blood 2007;110: 2242-9.

22. Soverini S, Colarossi S, Gnani A, et al. Contribution of ABL kinase domain mutations to imatinib resistance in different subsets of Philadelphia-positive patients. Clin Cancer Res 2006;12:7374-9.

23. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-55.

24. Hasford J, Pfirrmann M, Hehlmann R, et al. A new prognostic score for survival of patients with chronic myeloid leukemia treated with interferon alfa. J Natl Cancer Inst 1998;90:850-8.

25. Branford S, Rudzki Z, Walsh S, et al. High frequency of point mutations clustered within the adenosine triphosphate-binding region of BCR/ABL in patients

with chronic myeloid leukemia or Ph-positive acute lymphoblastic leukemia who develop imatinib (STI571) resistance. Blood 2002;99:3472-5.
26. Hughes T, Deininger M, Hochhaus A, et al. Monitoring CML patients responding to treatment with tyrosine kinase inhibitors: review and recommendations for harmonizing current methodology for detecting BCR-ABL transcripts and kinase domain mutations and for expressing results. Blood 2006;108:28-37.
27. Porkka K, Khoury HJ, Paquette RL, Matloub Y, Sinha R, Cortes JE. Dasatinib 100 mg once daily minimizes the occurrence of pleural effusion in patients with chronic myeloid leukemia in chronic phase and efficacy is unaffected in patients who develop pleural effusion. Cancer 2010;116:377-86.
28. Hasford J, Pfirrmann M, Hehlmann R, et al. Prognostic factors. In: Carella AM, Daley GQ, Eaves CJ, Goldman JM, Hehlmann R, eds. Chronic myeloid leukemia: biology and treatment. London: Martin Dunitz, 2001:205-23.
29. Sokal JE, Cox EB, Baccarani M, et al. Prognostic discrimination in "good-risk" chronic granulocytic leukemia. Blood 1984;63:789-99.
30. Saglio G, Kim D-W, Issaragrisil S, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. N Engl J Med 2010. DOI: 10.1056/NEJMoa0912614.
31. Cortes J, Talpaz M, O'Brien S, et al. Molecular responses in patients with chronic myelogenous leukemia in chronic phase treated with imatinib mesylate. Clin Cancer Res 2005;11:3425-32.
32. Iacobucci I, Saglio G, Rosti G, et al. Achieving a major molecular response at the time of a complete cytogenetic response (CCgR) predicts a better duration of CCgR in imatinib-treated chronic myeloid leukemia patients. Clin Cancer Res 2006;12:3037-42.
33. Press RD, Love Z, Tronnes AA, et al. BCR-ABL mRNA levels at and after the time of a complete cytogenetic response (CCR) predict the duration of CCR in imatinib mesylate-treated patients with CML. Blood 2006;107:4250-6.
34. Paschka P, Müller MC, Merx K, et al. Molecular monitoring of response to imatinib (Glivec) in CML patients pretreated with interferon alpha: low levels of residual disease are associated with continuous remission. Leukemia 2003;17:1687-94.