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REVIEW

Systematic review of dasatinib in chronic myeloid leukemia

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Abstract: Dasatinib is a dual tyrosine kinase inhibitor active against *ABL* and Src family kinases, and is approved for the treatment of chronic myeloid leukemia (CML) patients in chronic, accelerated, or blast phase with resistance or intolerance to imatinib therapy, for newly diagnosed chronic phase patients, and for adults with Philadelphia chromosome-positive acute lymphoblastic leukemia who have become resistant to or intolerant of other treatments. This review presents clinical data regarding different trials involving CML patients in different phases of the disease. Six-year follow-up of the Phase III dose-optimization study are described, showing overall survival of 71% with the current approved dose of 100 mg once daily. Three-year results of the randomized Phase III DASISION (DASatinib vs Imatinib Study In Treatment-Naïve CML patients) trial confirmed that dasatinib 100 mg once daily was superior to standard-dose imatinib in terms of achieving a faster and deeper molecular response, with similar activity regardless of baseline prognostic score.

Keywords: chronic myeloid leukemia, acute lymphoblastic leukemia, dasatinib

Introduction

Dasatinib is an oral dual tyrosine kinase inhibitor active against ABL and Src family kinases. It is able to inhibit BCR-ABL1 with a half maximal inhibitory concentration of <1 nmol/L and is also active against c-KIT, PDGFR, and EPHA2, as well as against members of the Src kinase family, such as Lyn, Yes, and Src, with a half maximal inhibitory concentration of 0.5 nmol/L.[1] The structure of dasatinib is based on a chemical scaffold different from that of imatinib, and has a 325-fold greater potency,[2] with the ability to bind both the inactive and active conformations of the ABL kinase domain. Dasatinib is active against at least 100 of the BCR-ABL1 mutations known to confer resistance to imatinib that have been tested to date, (including many in the p-loop region), except for the T315I mutation and a few other mutations (V299L, F317L/V, and T315A).[3] Dasatinib is able to block downstream intracellular signaling pathways activated by BCR-ABL1 in vitro, including signal transducer and activator of transcription 5 (Stat5), with downregulation of Stat5 target gene expression and the mitogen-activated protein kinase pathway.[4,5] Notably, dasatinib is not a substrate of multidrug resistance protein-1, an efflux protein expressed on normal and leukemic hematopoietic stem cells.[6] Unlike imatinib, dasatinib is not a substrate for OCT-1, and its activity is unaffected by overexpression of OCT-1.[7] Dasatinib has been approved for the treatment of patients with chronic phase disease at a recommended dose of 100 mg once daily (regardless food assumption), and for patients with accelerated phase and blast phase at a recommended dose of 140 mg once daily. It is possible to assume the drug regardless

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food assumption. This review summarizes the relevant clinical data from several trials using dasatinib first-line and second-line in patients with chronic myeloid leukemia (CML).

Search strategy

A search on ClinicalTrials.gov using the term "dasatinib" yielded 216 studies, whereas the terms "dasatinib CML" identified only 65 studies, not all of which were active, with some only proposed but not yet recruiting patients. All published clinical trials that enrolled patients treated with dasatinib were reviewed. We also searched the PubMed database for pertinent English language publications using the following terms: "dasatinib", "chronic myeloid leukemia", "chronic myeloid leukaemia", and "clinical trial". Relevant articles and abstracts were identified as those reporting Phase I, II and III clinical trials. Conference proceedings published by the American Society of Hematology, American Society of Clinical Oncology, and European Hematology Association were also searched from 2000 onwards.

Phase I clinical trial

Eighty-four patients with chronic (n = 40) or advanced phase (n = 44) CML and resistant or intolerant to imatinib were enrolled in a Phase I dose-finding study. Dasatinib was tested in a dose range of 15–180 mg/day on a once-daily or twice-daily schedule. The maximum tolerated dose of dasatinib was identified to be 70 mg twice daily. Previous therapies included interferon (in >90% of patients), stem cell transplantation (4%), and/or high doses of imatinib (>60%). After a minimum follow-up of 27 months, the rate of complete hematologic response in chronic phase patients, post-imatinib failure, was 91%, the rate of major cytogenetic response was 51%, and the rate of complete cytogenetic response was 44%. No differences were found in rates of complete cytogenetic response for the once-daily and twice-daily schedules (45% and 43%, respectively). The 36-month progression-free survival rate was 87% and overall survival was 94% for patients who achieved a major cytogenetic response within the first year of dasatinib therapy. For patients who did not achieve a major cytogenetic response within the first year, 36-month progression-free survival was 28% and overall survival was 68%. Grade 3/4 hematologic side effects included neutropenia in 50% of patients and thrombocytopenia in 60%.[8,9]

START Phase II program in patients resistant or intolerant to imatinib

In the Phase II START-C trial, dasatinib was tested as a single agent at a dose of 70 mg twice daily in 387 patients with resistance (75%) or intolerance (25%) to imatinib. Fifty-five percent of patients received high doses of imatinib and 10% were included after failure of bone marrow transplantation. Ninety percent of patients achieved a complete hematologic response, and a major cytogenetic response was achieved in 62% of patients, 88% of whom maintained their response at the 24-month follow-up. The complete cytogenetic response rate was 53%, with 90% of patients maintaining their response at 24 months. Two-year progression-free survival was 80% and overall survival was 94%. BCR-ABL1 mutations were detected in 160 of 363 patients (44%), with G250E and T315I mutants being the most frequently found.[10] No differences in overall response rate were observed in patients with BCR-ABL1 mutations at baseline, in particular for p-loop mutations. A subanalysis was conducted by Branford et al on the emergence of new detectable mutations in 479 patients treated with dasatinib after imatinib failure, and development of new mutations, including T315A, F317L, and V299L, was rare (13%).[11] Grade 3/4 adverse hematologic events occurring in the first 2 years consisted mainly of neutropenia (50%) and thrombocytopenia (49%). Adverse nonhematologic events observed in this trial (diarrhea, headache, rash, and fatigue) were similar to those observed in the Phase I studies, and were of grade 3/4 in <5% of patients, with a slight increase in prevalence between the first and second year of follow-up.[12] The incidence of pleural effusion was 22%, with the majority of cases being grade 1/2 and mostly occurring during the first year, with a slight increase to 25% at the 2-year follow-up. Grade 3 pleural effusions were recorded in less than 10% of patients, and no grade 4 effusions were observed.[12] The results of this trial also indicated a lack of cross-intolerance between imatinib and dasatinib, demonstrating the efficacy of dasatinib in imatinib-resistant and imatinib-intolerant patients, even if mutated.

The START-R trial included imatinib-resistant patients who failed to respond to standard-dose imatinib and were randomized at a ratio of 2:1 to receive dasatinib 70 mg twice daily or imatinib 800 mg daily.[13] Results reported after a follow-up of 2 years showed a complete hematologic response in 93% of patients treated with dasatinib and in 82% of those treated with high-dose imatinib. A higher major cytogenetic response rate was observed in the dasatinib arm compared with the imatinib arm (53% versus 33%; $P = 0.017$), with a complete cytogenetic response rate of 44% and 18%, respectively ($P = 0.0025$). At the follow-up reported at 18 months, 90% of patients in the dasatinib arm and 74% of those in the high-dose imatinib arm had maintained a major cytogenetic response. Major molecular

responses were also more frequently seen in dasatinib-treated patients than in those treated with high-dose imatinib (29% versus 12%; $P = 0.028$). The most frequent grade 3/4 adverse events with dasatinib were neutropenia, thrombocytopenia, and leukopenia. Nonhematologic adverse events reported were usually grade 1/2, with the most frequent grade 3/4 events being diarrhea, fatigue, and headache.[13] The results of START-R showed definitively that switching to a second-generation drug rather than increasing the dose of imatinib is a better strategy for resistant CML patients.

The START-A trial recruited 174 accelerated phase CML patients (161 resistant to, and 13 intolerant to, imatinib). At 8-month follow-up, the complete cytogenetic response rate was 24%. After a minimum 14 months of follow-up, major and complete hematologic responses were achieved in 64% and 45% of patients treated with dasatinib 70 mg twice daily, and major and complete cytogenetic responses were obtained in 39% and 32% of patients, respectively. No significant difference in terms of response rate was observed in terms of resistance or intolerance to imatinib, previous stem cell transplant, or presence of baseline mutations. One-year progression-free survival and overall survival rates were 66% and 82%, respectively. Grade 3/4 neutropenia and thrombocytopenia occurred in 76% and 82%, respectively; diarrhea occurred in 52% of patients, being of grade 3/4 severity in 8%, and pleural effusion occurred in 27%, being of grade 3/4 severity in 5%.[14]

The START-B and START-L programs enrolled 74 myeloid blast phase and 42 lymphoid blast phase patients.[15] After 8 months of follow-up, major hematologic response rates were 34% and 31%, respectively, in myeloid and lymphoid blast phase patients, whereas major cytogenetic response rates were 31% and 50%, with complete cytogenetic response rates of 27% and 43%. Adverse events led to discontinuation in 11% and 2% of myeloid and lymphoid blast phase patients, respectively. Baseline *BCR-ABL* mutation data were available for 95% of patients. Very high imatinib resistance mutations (M244V, G250E, Y253H, E255K, E255V, T315I, F359V, H396R) were associated with the lowest response rates to dasatinib. For the myeloid blast phase patients, the most frequently reported adverse events were diarrhea (36%), pleural effusion (28%), peripheral edema (19%), and dyspnea (18%), with 14% being grade 3/4 pleural effusion. Common side effects reported in lymphoid blast phase patients were diarrhea (31%), fatigue (29%), and nausea and vomiting (24%). Ottmann et al reported the results for 36 patients with Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia who participated in the START-L trial,[16] in whom the complete cytogenetic response rate at the 8-month follow-up was 58%; 67% of these patients achieved a major hematologic response, and five experienced disease progression. A T315I mutation was found at baseline in six patients and was associated with a worse response, but no difference in response rate was found for patients with resistant mutations in comparison with the whole patient population. The most frequently reported adverse events of any grade were diarrhea (31%), pyrexia (25%), and nausea (22%), whereas the most common grade 3/4 events were febrile neutropenia (11%), diarrhea (8%), and asthenia (8%), as shown in Table 1. Dasatinib is a valid option for advanced phases of disease because of its broad spectrum of inhibition, even if responses are not durable in most patients treated for blast crisis.

Phase III dose-optimization trials

The international, open-label, four-arm CA180-034 study (the so-called "dose-optimization trial") enrolled 670 patients who were resistant or intolerant to prior imatinib therapy, and randomized them to receive dasatinib 140 mg once daily, 70 mg twice daily, 100 mg once daily, or 50 mg twice daily. A recent 6-year follow-up of this study was presented at the 2012 meeting of the European Haematology Association.[17]

Table 1 Summary of responses in chronic phase patients treated with dasatinib as second-line therapy

References	Study	Number of patients/ type of treatment	CHR	CCR	MMR	OS	PFS
Hochhaus et al[12]	START-C*	387 (dasatinib 70 mg BID)	90%	53%	–	94%	80%
Kantarjian et al[13]	START-R**	101 (dasatinib 70 mg BID)	93%	44%	29%	nr	86%
	START-R	49 (high-dose imatinib 800 mg)	82%	18%	12%	nr	65%
Rea et al[18]	CA180-034***	167 (dasatinib 100 mg QD)	92%	50%	42%***	71%***	49%***
		168 (dasatinib 70 mg BID)	88%	53%	43%	70%***	47%***
		167 (dasatinib 140 mg QD)	87%	50%	42%	77%***	40%***
		168 (dasatinib 50 mg BID)	92%	49%	41%	74%***	51%***

Notes: *2-year follow-up; **2-year follow-up; ***6-year follow-up.
Abbreviations: QD, once daily; BID, twice daily; CHR, complete hematologic remission; CCR, complete cytogenetic remission; MMR, major molecular response; OS, overall survival; PFS, progression-free survival.

Based on preliminary results, the approved dose for chronic phase patients resistant to, or with a suboptimal response or intolerance to, imatinib therapy was changed to 100 mg once daily from the initially approved dose of 70 mg twice daily. The results of the 72-month follow-up of this study showed a progression-free survival of 49% and an overall survival of 71% for patients treated with dasatinib 100 mg once daily. Baseline patient characteristics were similar in the groups allocated to the different dose regimens, with a median CML duration of longer than 50 months, previous treatment with high-dose imatinib in more than 30% of patients, and a small cohort of patients who had failed previous allogeneic transplant. At the 72-month follow-up, similar outcomes were found in all arms of the trial, with a complete hematologic response achieved in 92% and complete cytogenetic remission in 50% of the 100 mg once daily arm; the last molecular assessment for major molecular response (BCR-ABL1/ABL1 transcripts $< 0.1\%$) showed a response rate of 42% in this arm. Progression to more advanced phases occurred at a consistently low rate of 1.2% for the first 3 years in the cohort of patients treated with 100 mg once daily, with no further progression in the subsequent year. Overall, ten patients showed disease transformation, with nine becoming resistant and one becoming intolerant to imatinib, with the majority of events occurring during the first 3 years of follow-up. Landmark analysis of progression-free survival was conducted at 4 years according to the response at 6 months in patients treated with 100 mg once daily, in patients with a major molecular response, in those with a complete cytogenetic response (but not a major molecular response), in those with a partial cytogenetic response, and in those with or without a minimal/minor response. Ninety-three percent of patients receiving 100 mg once daily who achieved a major molecular or complete cytogenetic response at 6 months were progression-free at 48 months versus 67% of those with a partial cytogenetic response and 41% of those with a minor/absent cytogenetic response. Landmark analysis of progression-free survival according to response at 12 months showed a similar trend, with 93% of patients who achieved a major molecular response at 12 months being progression-free at 48 months versus 87% of patients who achieved a complete cytogenetic response or major molecular response in the 100 mg once daily arm. A landmark analysis of progression-free survival according to response at 12 months showed similar results, with 94% of patients who achieved a major molecular response being progression-free versus 82% of those who achieved a complete cytogenetic response.[18]

Follow-up of the CA180-034 study at 72 months showed that drug-related nonhematologic side effects usually occurred in the first 24 months and were typically mild to moderate (grade 1/2). The most frequent adverse events were headache, diarrhea, and fatigue. Pleural effusions occurred more often within the first 24 months of treatment, ie, 15% by 24 months, 7% at 24–36 months, and 2% beyond 36 months, with a final rate at 6 years of 25.3%. No grade 4 pleural effusions were observed. Similar to nonhematologic toxicity, hematologic side effects occurred early during treatment (in the first 12 months), with grade 3/4 neutropenia occurring in 33% of patients by 12 months, in 1.8% at 12–24 months, in 0.6% at 24–36 months, and in none at 36–48 months, with a final rate of 36%. Grade 3/4 thrombocytopenia occurred in 22% of patients by 12 months, in 1.2% at 12–24 months, in 1.2% at 12–36 months, and in none at 36–48 months, with a final rate of 24%. Thirty-one percent of patients enrolled in the 100 mg once daily arm remained in the study, with the main reasons for discontinuation being disease progression (in 21%) and drug toxicities (in 21%), as shown in Table 1.[18]

A randomized Phase III trial assessed the efficacy and safety of 140 mg once daily versus 70 mg twice daily in advanced phase CML or Ph+ acute lymphoblastic leukemia that was resistant or intolerant to imatinib. Patients were randomized 1:1 to receive dasatinib 140 mg or 70 mg according to the type of blast phase (lymphoid or myeloid). In myeloid blast phase patients, the major hematologic rate remission was 28% with both regimens, whereas in lymphoid blast phase patients, the rate was 42% with a 140 mg once daily dose and 32% with a 70 mg twice daily dose. The major cytogenetic remission rate in myeloid blast phase patients was 25% with a once-daily regimen and 28% with a twice-daily regimen, and was 50% and 40%, respectively, in the lymphoid blast phase. Overall survival at 24 months was 24% and 28% in myeloid blast phase with 140 mg once daily and 70 mg twice daily, respectively, and 21% and 16%, respectively, in lymphoid blast phase. Analysis of the safety profile showed improved tolerability with the once-daily regimen.[19]

Trials in newly diagnosed chronic phase CML patients

Phase II MDACC trial

In this trial, 93 chronic phase CML patients were randomly assigned to receive dasatinib 100 mg once daily (n = 62) or 50 mg twice daily (n = 31). There were no significant differences between the two treatment groups in terms of baseline characteristics, with a median patient age of 47 years and

a low Sokal risk in 81% of the patients enrolled. Nineteen patients had been treated with imatinib prior to enrolment. All patients who had not achieved a hematologic response at the time of starting dasatinib went on to achieve a complete hematologic response, and overall, the complete hematologic response rate was 98%, with 95% of patients achieving a complete cytogenetic response. After 4 years of follow-up, 86% of patients had achieved a major molecular response and 67% had achieved a complete molecular response. No difference in responses was observed between the different treatment schedules. After 4 years of follow-up, event-free survival was 93%, whereas overall survival and progression-free survival were both 100% (Table 2). Regarding nonhematologic toxicity, muscle and bone pain (6%), fatigue (6%), dyspnea (5%), and neurologic disturbances (5%) were the major grade 3/4 events. Pleural effusion occurred in 13% of patients, but was grade 3 (2%) in only one patient. Pleural effusion occurred in two of 31 patients on the 100 mg once-daily regimen and in six of 31 patients on the 50 mg twice-daily regimen. In terms of hematologic toxicity, 21% of patients experienced grade 3/4 neutropenia, 10% developed grade 3/4 thrombocytopenia, and 6% had grade 3/4 anemia. Overall, 48% of patients required temporary drug suspension (mostly for pleural effusion, dyspnea, and/or headache) and 35% needed dose reduction. Three patients required discontinuation of dasatinib as a result of pleural effusion (n = 2) or prolonged cytopenia (n = 1).[20] The results of this trial show for the first time that dasatinib is a valid option for newly diagnosed CML patients, with a safety profile similar to that observed when the drug is used as second-line therapy.

DASISION trial: 3-year follow-up

DASISION (DASatinib vs Imatinib Study In Treatment-Naïve CML patients) was a multicenter Phase III trial which compared the efficacy of dasatinib 100 mg once daily versus a standard 400 mg dose of imatinib. In total, 519 patients were enrolled and randomized 1:1 according to Hasford risk (259 patients to dasatinib and 260 to imatinib).[20] The primary endpoint of the study was achievement of a confirmed complete cytogenetic response, defined as a documented complete cytogenetic response on two consecutive assessments at least 28 days apart. Secondary endpoints were achievement of a major molecular response at any time, times to confirmed complete cytogenetic response and to major molecular response, rates of complete cytogenetic response and major molecular response by 12 months, progression-free survival, and overall survival.[21–23]

The demographic characteristics and risk stratification of the patients enrolled were reported to be well balanced between the two cohorts of patients treated with dasatinib or imatinib. After 3 years, 71% of patients remained on treatment in the dasatinib arm and 69% in the imatinib arm. Discontinuation occurred in 11% of patients in the dasatinib arm because of drug toxicity and in 7% because of disease progression (definition of progression-free survival in this study, as in the dose-optimization trial, included not only progression to accelerated and blast phases, but also loss of complete hematologic response, loss of major cytogenetic response, increasing white blood cell counts, and death of any cause) compared with 6% and 7%, respectively, in the imatinib arm. Three percent of patients treated with dasatinib and 5% of those treated with imatinib experienced treatment failure.

The results of this study were reported according to the intention-to-treat population. At 24-month follow-up, the confirmed complete cytogenetic response rate was higher in the dasatinib arm (86%) than in the imatinib arm (82%). Regarding the secondary endpoint, the rate of major molecular response at 3-year follow-up was higher in patients treated with dasatinib (68%) than in those treated with imatinib (55%), irrespective of Hasford risk at baseline. The cumulative incidence of MR4 (BCR-ABL/ABL ratio $<$ 0.01% IS) and MR4.5 (BCR-ABL/ABL ratio $<$ 0.0032% IS) at 3 years was 35% versus 22% and 22% versus 12% for dasatinib and imatinib, respectively. Transformation to

Table 2 Dasatinib in first-line treatment for newly diagnosed patients with chronic phase CML

References	Study	Number of patients/ type of treatment	CHR	CCR	MMR	CMR	MR4	MR4.5	OS	PFS	EFS
Pemmaraju et al[19]	MDACC*	93 (dasatinib random 1:1 100 mg QD versus 50 mg BID)	98%	95%	87%	67%	–	–	100%	100%	93%
Kantarjian et al[20]	DASISION**	259 (dasatinib 100 mg QD)	NR	86%	68%	–	35%	22%	93.7%	91%	–
		260 (imatinib 400 mg)	NR	82%	55%	–	22%	12%	93.2%	90.9%	–
Radich et al[28]	S0325	123 (dasatinib 100 mg)	81%	84%	59%	–	27%	21%	97%	93%	–
		123 (imatinib 400 mg)	82%	69%	44%	–	21%	15%	97%	90%	–

Notes: *4-year follow-up; **3-year follow-up.

Abbreviations: CHR, complete hematologic remission; CCR, complete cytogenetic remission; CML, chronic myeloid leukemia; MMR, major molecular response; OS, overall survival; PFS, progression-free survival; EFS, event-free survival; CMR, complete molecular response; MR4, BCR-ABL/ABL $<$ 0.01%IS; MR4.5, BCR-ABL/ABL $<$ 0.0032% IS; NR, not reported.

blast phase occurred in eight of 259 patients (1.9%) in the dasatinib arm and in 13 of 260 patients (3.5%) in the imatinib arm. Estimated progression-free survival at 3 years was 91% in the dasatinib arm and 90.9% in the imatinib arm, whereas estimated overall survival at 3 years was 93.7% in the dasatinib arm and 93.2% in the imatinib arm (Table 2). Fourteen patients in each arm had newly detected mutations on treatment, with nine patients in the dasatinib arm having a T315I mutation.

The incidence of grade 3/4 neutropenia was 24% in the dasatinib arm and 20.9% in the imatinib arm, and the incidence of thrombocytopenia was higher with dasatinib (19.4%) than with imatinib (11.2%). Grade 3/4 anemia occurred in 11.6% in the dasatinib arm and in 8.5% in the imatinib arm. The majority of adverse hematologic events occurred during the first few months of treatment. A low rate of grade 3/4 adverse nonhematologic events was observed in patients treated with dasatinib, and consisted of diarrhea, headache, fatigue, and musculoskeletal pain. Fluid retention (all grades) was observed in 14% of patients treated with dasatinib and in 42.3% of patients treated with imatinib. Pleural effusions were recorded only in the dasatinib arm, in 17.5% of patients, but in the majority of cases were grade 1/2, with less than 1% being grade 3/4. Gastrointestinal bleeding occurred in 5% of patients in both the dasatinib and imatinib arms. With regard to laboratory abnormalities of interest, only hypophosphatemia was reported, and occurred in 7% of patients treated with dasatinib and in 28.3% of those treated with imatinib. A similar incidence of electrocardiographic changes occurred in both arms, although the median change in QTc interval was smaller with dasatinib (3.0 msec) than with imatinib (8.2 msec).[24]

Information on specific toxicity of the drug when used first-line suggested that evaluation of baseline comorbidities and subsequent strict monitoring of treated patients could avoid major side effects, such as grade 3/4 thrombocytopenia and pleural effusion. Weekly outpatient visits for the first two months were arranged, which allowed physicians to treat thrombocytopenia at first occurrence and enabled early recognition of cough, dyspnea, and chest pain in patients with predisposing comorbidities, so that drug-related pleural and pericardial effusions could be easily managed. Dasatinib has recently been associated with development of pulmonary hypertension, defined as increased vascular resistance and mean pulmonary artery pressure $>$ 25 mmHg at rest or $>$30 mmHg on exercise. Several case reports have suggested that the diagnosis is certain only after right heart catheterization, and that was requested a discontinuation of the drug. In DASISION, three patients were diagnosed with pulmonary hypertension (incidence 1.2%), but only one underwent right heart catheterization, with a negative result. In a retrospective analysis of 2800 cases treated with dasatinib, only one patient was reported to have pulmonary hypertension.[25] However, a French group reported a series of nine cases with moderate to severe precapillary pulmonary hypertension after treatment with dasatinib, with a female prevalence and hemodynamic improvement after discontinuation of the drug.[26] Eighty-four percent of patients in the dasatinib arm achieved a BCR-ABL/ABL ratio of $<$10% at 3 months from the start of treatment, compared with 64% of patients in the imatinib arm. Eight-one percent of patients who received dasatinib had a cytogenetic response and 68% had a complete cytogenetic response. Early evaluation of molecular response at 3 months correlated with worse progression-free survival and overall survival in patients with a ratio $>$ 10%.[27]

S0325 US trial

The one-year results were recently reported for the Phase III open-label, randomized S0325 trial by four cooperative US groups (Southwest Oncology Group, Eastern Cooperative Oncology Group, Cancer and Leukemia Group B, National Cancer Institute of Canada Clinical Trials Group) that compared dasatinib 100 mg daily versus imatinib 400 mg daily in newly diagnosed chronic phase CML.[26] A total of 253 patients were enrolled and randomized according to Hasford risk. The rationale of the trial provided the opportunity to escalate the daily dose of imatinib to 600 mg or dasatinib to 140 mg in the event of Ph+ metaphases $>$ 95% at 6 months. The primary endpoint of the study was achievement of a more than 4 log reduction in *BCR-ABL1* transcripts at 12 months. Five patients were not eligible because of absence of the Ph+ chromosome, accelerated phase disease, or cardiac symptoms. No particular differences in patient characteristics were shown between the two arms, except that, unlike in DASISION, 30% of the patients in the S0325 study were classified as being high risk, and patients were younger in the dasatinib arm.

At one-year follow-up, no differences were reported for complete hematologic response (81% for dasatinib and 82% for imatinib). Of 131 patients with evaluable cytogenetic data, the complete cytogenetic response rate was 84% for dasatinib versus 69% for imatinib. In terms of molecular responses, the major molecular response rate after one year was 59% for dasatinib versus 44% for imatinib, the MR4 rate was 27% for dasatinib versus 21% for imatinib, and the

MR4.5 rate was 21% for dasatinib versus 15% for imatinib. Mutational status was evaluated in 25 patients with resistant disease, and only three mutations were found, including one patient in the dasatinib arm with V299L and two patients with M244V and E453K in the imatinib arm. There was no difference between the groups in overall survival (97% for both arms), whereas in terms of progression-free survival (93% for dasatinib versus 90% for imatinib), six patients had progression with dasatinib and nine patients with imatinib, but only two patients had confirmed blast crisis.

With regard to toxicity, 15% of patients in the dasatinib arm experienced grade 4 toxicity compared with 2% in the imatinib arm. The most common adverse events on dasatinib were grade 3/4 thrombocytopenia (18% versus 8% in the imatinib arm) and pleural effusion (11%, with <2% being grade 3 in the imatinib arm). During the first year, 16 patients in the dasatinib arm discontinued therapy and 12 patients discontinued in the imatinib arm. The dose was decreased in nine patients on dasatinib and in four patients on imatinib, whereas the dose was escalated in three patients (one on dasatinib and two on imatinib). The results of this trial were similar to those of DASISION, in terms of dasatinib being able to induce more rapid responses but at the expense of increased toxicity (Table 2).[28]

Trials in Ph+ acute lymphoblastic leukemia

Dasatinib has been tested as front-line treatment in Ph+ acute lymphoblastic leukemia as a single agent or in association with chemotherapy. Ravandi et al described the results of a Phase II study in which dasatinib was administered as 50 mg twice daily for the first 14 days of each of eight cycles of alternating hyper-CVAD (hyperfractionated cyclophosphamide, doxorubicin, vincristine, and dexamethasone) and high-dose cytarabine and methotrexate. Thirty-five patients of median age 53 years were treated, and 94% achieved complete remission, with two patients dying as a result of infection before evaluation of response. Twenty-seven patients achieved a cytogenetic response after the first cycle, but four patients had persistent Ph+ metaphase. Twenty patients achieved complete molecular remission at a median of 14 weeks and a further seven patients achieved a major molecular response at a median of 11 weeks. Monitoring of residual disease was negative by flow cytometry in 29 of 33 patients at a median of 3 weeks. After a median follow-up of 14 months, median disease-free survival and overall survival were not reached, with an estimated 2-year overall survival of 64%. Sixteen episodes of bleeding and eight episodes of pleural effusion, infection, deep vein thrombosis and pulmonary emboli, diarrhea, and metabolic abnormalities were reported.[29]

Dasatinib was also tested as a single agent in the GIMEMA LAL1205 trial of induction therapy with steroids for 84 days and free post-remission therapy. All 53 evaluable patients achieved complete hematologic remission, 92.5% of these at day 22; at this time point, 10 out of 53 patients achieved a 3 log reduction at molecular level. Overall survival and disease-free survival rates were 69% and 51%, respectively, at 20 months, with better results in terms of disease-free survival for patients who showed a molecular response at day 22. No deaths or relapses occurred during induction therapy. Twenty-three of the 53 patients relapsed after completion of induction and, of these, 12 had T315I onset. Overall, treatment was well tolerated. Four patients discontinued because of toxicity (only one case of pleural effusion grade 1–2). Another case of pleural effusion was recorded in a patient who continued treatment with dasatinib.[30]

Future directions

A major issue which is still a matter of debate is the potential effects of tyrosine kinase inhibitors on stem cells and the possibility of complete eradication of disease. It has been reported that, although dasatinib is more effective than imatinib within the stem cell compartment, the most primitive quiescent cells also appear to be resistant to this drug.[31] Src kinase expression is increased in CD34+ cells and in the CD34+CD38− fraction in all phases of CML. Dasatinib is able to inhibit P mitogen-activated protein kinase (MAPK9, Akt, and STAT5) in CML progenitors, but does not alter the level of apoptosis-regulating proteins in CD34+ cells.[32] Attempts to target a quiescent fraction have been made in association with dasatinib or with similar drugs; for example, a cytotoxic farnesyl transferase inhibitor (BMS-214662) was tested alone or in combination with dasatinib. This drug was able to induce apoptosis of both proliferating and quiescent stem cells in different phases of the disease and also in wild-type and mutant cell lines, including a cell line with T315I.[33] Bellodi et al reported that suppression of autophagy by pharmacologic inhibition (chloroquine) or by RNA interference of autophagy genes enhanced apoptosis of imatinib. A combination of autophagy inhibitors and dasatinib or nilotinib allowed near complete eradication of Ph+ stem cells.[34] Sabutoclax, a pan BCL2 inhibitor, was recently tested in quiescent stem cells, and was found to be able to sensitize the stem cell compartment to tyrosine kinase inhibitors, with the aim of eradicating leukemia stem cells and thereby overcome the problem of resistance.[35]

Conclusion

The results of different trials testing dasatinib as a second-line agent have shown that this drug is a valid option for imatinib-resistant or intolerant chronic phase patients. The results of the international Phase III dose-optimization study demonstrated that an intermittent treatment regimen using a starting dose of 100 mg once daily is the safest and most effective dose, and this is now recommended for chronic phase patients. Recent 6-year follow-up of this study provides further evidence that the efficacy of dasatinib is maintained, with an estimated overall survival of 71% and a progression-free survival of 49%. Dasatinib was tested at the same dose as that used in first-line treatment for newly diagnosed patients, and intermittent therapy with 100 mg once daily was shown to induce higher and faster cytogenetic and molecular responses, with a 4 or 4.5 log reduction in comparison with imatinib. After 3-years of follow-up, no differences in overall survival or progression-free survival were found between dasatinib and imatinib, and longer follow-up is needed. In conclusion, dasatinib is a possible option as second-line therapy in patients who are resistant or intolerant to imatinib, and recent follow-up of trials that tested the drug as a possible first-line option have shown dasatinib to be an option for newly diagnosed CML patients.

Disclosure

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