Dasatinib
In Chronic Myeloid Leukemia and Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia

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Abstract

Dasatinib is a small-molecule inhibitor of multiple tyrosine kinases, including BCR-ABL, SRC, c-KIT, ephrin A receptor and platelet-derived growth factor-β receptor kinases, at nanomolar concentrations. In vitro, dasatinib is 325-fold more potent than imatinib against cells expressing wild-type BCR-ABL.

The efficacy and tolerability of oral dasatinib has been established in the START phase II trials in adults with chronic myeloid leukemia (CML) or Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph-positive ALL) who were intolerant or resistant to imatinib, and optimal dasatinib dosage regimens were identified in phase III randomized trials.

In patients with chronic phase CML, the major cytogenetic response rate in the START-C trial (median follow-up 15.2 months) was 59% with dasatinib, and in the randomized START-R trial (median follow-up 15 months), was greater with dasatinib than with high-dose imatinib (52% vs 33%). Major hematologic response rates with dasatinib were 63% in patients with accelerated phase CML (follow-up ≥9 months; START-A trial), 34% in patients with myeloid blast phase CML and 35% in those with lymphoid blast phase CML (follow-up ≥12 months; START-B and START-L trials), and 41% in patients with Ph-positive ALL (follow-up ≥12 months; START-L trial).

Based on phase III results, a once-daily dasatinib regimen is considered optimal in chronic phase CML (starting dosage 100 mg once daily), while a twice-daily regimen continues to be recommended in accelerated phase, myeloid blast phase or lymphoid blast phase CML and Ph-positive ALL (starting dosage 70 mg twice daily).

Adverse events were frequent in patients treated with dasatinib, but most were mild to moderate in severity. Grade 3/4 adverse events were uncommon and were clinically manageable.

Features and properties of dasatinib (Sprycel™)

| Indication |
| Treatment of adults with chronic, accelerated, or blast phase (advanced phase) chronic myeloid leukemia (CML) and resistance to or intolerance of prior therapy including imatinib, or Philadelphia chromosome (Ph)-positive acute lymphoblastic leukemia (ALL) and lymphoid blast CML and resistance to or intolerance of prior therapy |

| Mechanism of action |
| Inhibitor of multiple tyrosine kinases, including BCR-ABL, SRC, c-KIT, ephrin A receptor and platelet-derived growth factor-β receptor kinases |

| Dosage and administration |
| Recommended starting dosage |
| Chronic phase CML | 100 mg once daily |
| Accelerated, myeloid or lymphoid blast phase CML or Ph-positive ALL | 70 mg twice daily |
| Administration route | Oral |

| Pharmacokinetic profile |
| Time to peak plasma concentration | 0.5–3 h |
| Terminal elimination half-life | 5–6 h |

| Most frequent drug-related grade 3/4 adverse events in clinical trials (incidence ≥5%) |
| Hemorrhage (including gastrointestinal bleeding), fluid retention (including pleural effusion), febrile neutropenia, diarrhea, dyspnea |
Chronic myeloid leukemia (CML), which accounts for ≈15% of patients with leukemia, is a hematopoietic stem cell disorder that usually starts with an initial chronic phase. This is followed by progression over several years (3–5 years if left untreated) to the accelerated phase and finally results in a blast crisis. Blast phase CML (myeloid or lymphoid blast phase) is the least responsive to treatment. Most patients (~90%) are diagnosed in the chronic phase of the disease. CML occurs as a result of a reciprocal translocation between the long arms of chromosomes 9 and 22 to form the Philadelphia (Ph) chromosome. The Ph chromosome is also found in some cases of acute lymphoblastic leukemia (ALL). This translocation results in a chimeric protein product BCR-ABL, which is a constitutively active form of the ABL tyrosine kinase.

Imatinib, a small-molecule kinase inhibitor that inhibits the BCR-ABL kinase, has become the standard first-line treatment for newly diagnosed CML and is also indicated for use in chronic phase CML patients previously treated with interferon-α. In imatinib-treated patients, response rates are high in early (chronic phase) CML, with limited, and often transient, response rates in patients with more advanced disease. However, resistance to imatinib has been reported; some patients fail to respond to treatment, despite a therapeutic dosage regimen (primary resistance), whereas others may lose a previously established response (secondary resistance). For instance, in the IRIS (International Randomized Study of Interferon and ST1571) trial, the estimated relapse rate in imatinib recipients after a median follow-up of 5 years was 17%, and of the 31% of imatinib recipients who had discontinued first-line treatment or crossed over to the other treatment arm, ≈40% had done so because of an unsatisfactory therapeutic effect or disease progression. The underlying mechanisms of imatinib resistance include BCR-ABL gene mutations (most common cause), overexpression of BCR-ABL, and activation of BCR-ABL-independent pathways. Consequently, new agents that are more potent than imatinib and maintain activity against imatinib-resistant BCR-ABL gene mutations are required to treat patients who have failed imatinib therapy.

Dasatinib (Sprycel™), a small-molecule carboxamide derivative (structurally unrelated to imatinib) that is active against multiple tyrosine kinases, including BCR-ABL and SRC family kinases, is one such agent. This profile reviews the pharmacologic properties of orally administered dasatinib and its efficacy and tolerability in adult patients with chronic, accelerated, myeloid or lymphoid blast phase CML or Ph-positive ALL with resistance or intolerance to previous therapies (including imatinib).

1. Pharmacodynamic Profile

- Dasatinib inhibits the activity of various oncogenic kinases, namely BCR-ABL, SRC family (SRC, LCK, YES, FYN), c-KIT, ephrin A receptor and platelet-derived growth factor-β (PDGFR-β) receptor kinases, at nanomolar concentrations.
- X-ray crystal analysis of the structure of dasatinib-bound BCR-ABL kinase indicates that dasatinib binds to the ATP-binding site. Modelling studies indicate that dasatinib is able to bind to both the inactive and the active conformations of BCR-ABL kinase. In contrast, imatinib only binds to the inactive conformation of the enzyme (see figure 1). Consequently, dasatinib is likely to be effective against imatinib-resistant BCR-ABL mutations that have resulted in the destabilization of the inactive enzyme conformation.
- In vitro, dasatinib was 325-fold more potent than imatinib against CML cell lines expressing wild-type BCR-ABL kinase (concentration required for 50% inhibition [IC50] 0.6 vs 280 nmol/L).
- Dasatinib blocked downstream intracellular signalling pathways activated by BCR-ABL in vitro, including signal transducer and activator of transcription 5 (Stat5). This resulted in downregulation of Stat5 target gene expression, leading to inhibition of cell growth and induction of apoptosis. In addition, dasatinib potently inhibited the MAPK pathway in cell lines and primary CML cells.
- In vitro studies indicate that, while dasatinib targets an earlier progenitor population of CML stem cells than imatinib, the quiescent fraction of the stem cells appears to be resistant to both imatinib and dasatinib. Therefore, complete eradication of disease with dasatinib is not expected to occur in most patients with CML.
- Dasatinib is active against cell lines representing various forms of imatinib-sensitive and -resistant disease in in vitro studies. Dasatinib inhibited the proliferation of cells expressing wild-type BCR-ABL (IC50 0.8 nmol/L) and was similarly effective (IC50 0.6–11 nmol/L) against imatinib-resistant kinase domain mutants, with the exception of T315I, which involves a mutation at a critical contact residue for both imatinib and dasatinib.
- Growth of CML and ALL cell lines overexpressing BCR-ABL were inhibited by dasatinib. This included the proliferation of cells overexpressing SRC kinases (IC50 0.5 nmol/L).

1 The use of trade names is for product identification purposes only and does not imply endorsement.
induced apoptosis in BCR-ABL-expressing K562 cells that had become imatinib resistant as a result of SRC-family kinase activation[27] and reduced tumor growth of K562 cells over expressing SRC kinase in a nude mouse model. In contrast, imatinib had minimal effect on these tumors.[27]

- Dasatinib also inhibited the proliferation of cells and induced apoptosis in cells expressing mutant KIT kinases (IC₅₀ 5–150 nmol/L).[19]
- The survival of mice bearing CML tumors implanted at various sites, including the central nervous system, was prolonged by dasatinib treatment.[28-31] Dasatinib prevented the progression of CML from chronic to blast phase in a mouse model of the disease.[32]
- In vitro studies in hERG and Purkinje fibre assays have suggested that dasatinib may be associated with QT prolongation.[25] Although QT interval changes were not evident in a single-dose animal study, some patients in clinical trials had evidence of QT prolongation (section 4).[25]

2. Pharmacokinetic Profile

Published data regarding the clinical pharmacokinetics of dasatinib are limited; consequently, data included in this section have largely been obtained from the marketing authorization holder’s prescribing information.[25] The pharmacokinetics of dasatinib were examined in 229 healthy adult volunteers and 84 patients.[25]

- Following oral administration in patients, dasatinib is rapidly absorbed. Peak plasma concentrations (C_max) occur 0.5–3 hours after administration. The dasatinib area under the plasma concentration-time curve (AUC) increased proportionally over the dasatinib dosage range 25–120 mg twice daily.[25]
- In healthy volunteers, the mean AUC of dasatinib was in-creased by 14% compared with the fasted state when a single dose of dasatinib 100 mg was administered 30 minutes after a high-fat meal and by 21% when administered 30 minutes after a low-fat meal.[25,33] The effect of food on the pharmacokinetics of dasatinib is not considered to be clinically relevant.[25]

- Dasatinib has an apparent volume of distribution of 2505 L in patients, suggesting extensive distribution into tissues.[25] In vitro protein binding of dasatinib was ≈96%.[25]
- Dasatinib is extensively metabolized in the liver, predominantly by cytochrome P450 (CYP) 3A4.[25]
- In healthy volunteers administered a single dose of 14C-labelled dasatinib 100 mg, unchanged dasatinib accounted for 29% of circulating radioactivity in the plasma.[25,34] The metabolites of dasatinib are unlikely to play a role in the pharmacologic activity of this agent.[25]
- Linear elimination characteristics were observed over the dasatinib dosage range 25–120 mg twice daily in patients and the overall mean terminal elimination half-life of dasatinib was 5–6 hours.[25]
- Dasatinib and its metabolites are primarily eliminated in the feces. In healthy volunteers, mean total recoveries of total radioactivity within 10 days of administration of a single dose of 14C-labelled dasatinib 100 mg were approximately 4% in the urine and 85% in the feces.[25,34] Dasatinib is predominantly excreted as metabolites; 19% of a dose was recovered as the unchanged drug in feces and negligible amounts (0.1%) in urine.[25]

- In vitro studies have shown that dasatinib is a CYP3A4 substrate.[25] Systemic exposure to dasatinib may be increased if it is coadministered with drugs that are potent inhibitors of CYP3A4 activity (e.g. clarithromycin, erythromycin, itraconazole, ketoconazole, ritonavir, and telithromycin).[25]
- Conversely, exposure to dasatinib may be reduced when it is coadministered with agents that induce CYP3A4 activity (e.g. rifampicin [rifampin]). Dasatinib AUC was reduced by 82% in
healthy volunteers who were administered a single dose of dasatinib following 8 days of rifampicin 600 mg once daily.[25]

- Concomitant administration of dasatinib with H2 blockers/proton-pump inhibitors (e.g., famotidine or omeprazole) or antacids may reduce exposure to dasatinib. A single dose of famotidine administered 10 hours before dasatinib in healthy volunteers reduced dasatinib exposure by 61%.[28]

- Concomitant administration of aluminum hydroxide and a single dose of dasatinib in healthy volunteers reduced dasatinib AUC by 55%. However, administration of aluminum hydroxide 2 hours prior to dasatinib had no effect on exposure to dasatinib. Therefore, antacids should be given up to 2 hours before or 2 hours after administration of dasatinib, but not concomitantly.[25]

- Concomitant use of dasatinib and another CYP3A4 substrate (e.g., simvastatin) may increase exposure to the latter agent. In healthy volunteers, Cmax and AUC of simvastatin were increased by 37% and 20% when simvastatin was coadministered with a single dose of dasatinib 100 mg compared with simvastatin alone.[35] It is possible that this effect could be augmented after multiple doses of dasatinib.[125]

- As a consequence of these interactions, concomitant use of dasatinib and potent inhibitors or inducers of CYP3A4 activity or H2 blockers/proton-pump inhibitors is not recommended and caution is required when dasatinib is coadministered with CYP3A4 substrates that have a narrow therapeutic index.[25]

3. Therapeutic Efficacy

The efficacy of dasatinib has been assessed in a phase I trial,[36,37] five multicenter, phase II START (SRC-ABL Tyrosine kinase inhibition Activity Research Trials) studies,[38-42] and two phase III dose-optimization trials[43,44] in patients with CML or Ph-positive ALL who were resistant to or intolerant of imatinib.

Results discussed in this section focus on the most recent data from these trials (mostly presented as abstracts).[25,37,38,43-49]

In the phase I dose-ranging study, patients with chronic phase CML received dasatinib 15–180 mg/day on a once- or twice-daily schedule.[36,37] In four noncomparative phase II trials,[39-42] patients were treated with dasatinib 70 mg twice daily, while in the randomized phase II comparison with high-dose imatinib in patients who had previously failed therapy with imatinib 400–600 mg/day,[38] patients received dasatinib 70 mg or imatinib 400 mg twice daily. The dasatinib dosage was increased to 90 mg[38,39] or 100 mg[40-42] twice daily if there was a lack of response or reduced to 50 and then 40 mg twice daily in the event of toxicity.[38-42] The imatinib dose was reduced to 300 mg twice daily for toxicity in patients who had not previously received a 600 mg/day dosage.[38]

In the randomized comparison with imatinib, patients who experienced confirmed disease progression, lack of major cytogenetic response at 12 weeks or treatment intolerance (grade ≥3 nonhematologic toxicity or hematologic toxicity requiring multiple dose reductions) with either dasatinib or imatinib were permitted to cross over to the other treatment.[38]

The randomized, phase III dose-optimization trials were noninferiority trials comparing the efficacy and tolerability of once-daily versus twice-daily dasatinib treatment regimens.[25,45] In one trial,[41] patients with chronic phase CML who were resistant or intolerant to imatinib were randomized to receive dasatinib 100 mg once daily, 50 mg twice daily, 140 mg once daily or 70 mg twice daily. In the other trial,[42] patients with advanced phase CML or Ph-positive ALL were randomized to receive dasatinib 140 mg once daily or 70 mg twice daily. Dosage escalation for inadequate response or dosage reduction in the event of toxicity was permitted.

The definition of imatinib resistance varied according to diagnosis, but included failure to achieve complete hematologic response within 2 weeks to 3 months (depending on initial diagnosis and rate of disease progression), or any cytogenetic response within 6 months, or major cytogenetic response by month 12 at an imatinib dosage of 400 mg/day, or progression of disease after a previous cytogenetic or hematologic response.[50] Imatinib intolerance was defined as toxicity considered at least possibly related to imatinib ≤400 mg/day that led to treatment discontinuation or the ability to only tolerate imatinib dosages <400 mg/day.[50] Most patients in the trials were imatinib resistant (74% in START-C,[46] 93% in START-A,[48] =90% in START-B,[47] =90% [lymphoid blast phase CML][47] and 96% [Ph-positive ALL][49] in START-L, 100% in START-R[38] and =75% in the phase III trials in chronic phase CML)[25,45]. In all trials, patients were aged ≥18 years (median 46–59 years).[36,44]

Chronic phase CML was defined as <15% blasts in peripheral blood and bone marrow, <20% basophils in peripheral blood, <30% blasts plus promyelocytes in peripheral blood and bone marrow, platelets ≥100 000/mm3 unless thrombocytopenia was due to recent therapy and no extramedullary involvement other than liver or spleen.[36,38,39] Patients had accelerated phase disease if they had ≥15 but <30% blasts in the peripheral blood or bone marrow, ≥30% blasts and promyelocytes (but <30% blasts alone) in peripheral blood or bone marrow, or ≥20% basophils in the peripheral blood or bone marrow, or platelet count of <100 000/mm3 unrelated to therapy.[41] Blast phase CML was defined as ≥30% blasts in the peripheral blood or bone marrow and/or extramedullary leuemic infiltrates with peripheral blood blast cell morphology.[36] Patients with Ph-positive ALL had >30% lymphoblasts in the peripheral blood or bone marrow without previous evidence of chronic phase CML.[36]

The primary endpoint in trials in patients with chronic phase CML was the major cytogenetic response rate, while that in trials in patients with accelerated phase, myeloid blast phase and lymphoid blast phase CML, and Ph-positive ALL was the major
hematologic response rate. In the phase III dose-optimization trials, comparisons were made between once-daily and twice-daily treatment regimens for the respective endpoints.

Cyogenetic responses were calculated from the percentage of Ph-positive cells in metaphase in a bone marrow sample, with a complete response having 0% and a partial response having >0% to 35%. A major cytogenetic response (0–35%) represented a combination of partial and complete responses.

A complete hematologic response in patients with chronic phase CML comprised a white blood cell count at or below the institutional upper limit of normal (ULN), platelets <450,000/mm³, no blasts or promyelocytes in the peripheral blood, <5% myelocytes plus metamyelocytes in the peripheral blood, ≤ULN basophils in the peripheral blood and no extramedullary involvement. In patients with accelerated phase CML, blast phase CML or Ph-positive ALL, a complete response was the same as that in chronic phase CML except that absolute neutrophil count (ANC) was ≥1000/mm³, platelets were ≥100,000/mm³ and bone marrow blasts were ≤5%.

The definition of no evidence of leukemia for each patient group was the same as for a complete hematologic response except ANC was ≥500/mm³ and <1000/mm³, and/or platelets were ≥20,000/mm³ and ≤100,000/mm³. A major hematologic response represents a combination of complete hematologic response and no evidence of leukemia. All responses were to be maintained for at least 4 weeks.

Patient exclusion criteria included prior dasatinib therapy, imatinib therapy within 7 days of trial entry, or significant cardiovascular disease or a significant bleeding disorder unrelated to CML.

**Chronic Phase Chronic Myeloid Leukemia (CML)**

**Phase I Study**

The phase I dose-escalation study investigated the efficacy of dasatinib in 84 adult patients with chronic phase CML or Ph-positive ALL and imatinib resistance or intolerance. This review focuses on data at a minimum follow-up of 27 months in a subgroup of 45 patients with late chronic phase CML (available as an abstract). The median time from diagnosis of CML to trial entry was 8 years. Patients had previously been treated with interferon-α (91%), stem-cell transplantation (4%); 62% had received prior imatinib >600 mg/day.

- After a minimum 27 months’ follow-up, major and complete cytogenetic responses were seen in 51% and 44% of dasatinib recipients and the median duration of these responses had not been reached after a median treatment duration of 28 months. Complete cytogenetic response rates did not differ between once-daily and twice-daily treatment regimens (45% vs 43%).

- In patients who achieved a major cytogenetic response within the first 12 months of dasatinib treatment (n = 24), the 3-year progression-free survival rate was 87% and overall survival was 94%. In contrast, in the 21 patients who did not achieve a major cytogenetic response within the first 12 months of treatment, 3-year progression-free and overall survival rates were 28% and 68%.

- At ≥27 months’ follow-up, a complete hematologic response was seen in 91% of patients.

**START-C and START-R**

The START-C trial (CA 180013) investigated the efficacy of dasatinib in adult patients with chronic phase CML with imatinib resistance or intolerance. Data at a median follow-up of 8.3 months (186 evaluable patients) have been published. However, this review focuses on median follow-up data at 15.2 months for the full cohort of 387 patients available as abstracts. The median time from diagnosis of CML was 61 months. Patients had previously been treated with interferon-α (65%), stem-cell transplantation (10%), prior imatinib >600 mg/day (55%) and/or imatinib for a duration >3 years (53%). BCR-ABL mutations were present in 44% of patients.

The START-R trial (CA 180017) compared the efficacy of dasatinib with that of high-dose imatinib in imatinib-resistant adult patients with chronic phase CML. Data at a median follow-up of 15 months are available in the full cohort of 150 patients. The median time from initial diagnosis of CML was 59 months. All patients had been treated with imatinib (66% with imatinib 600 mg/day); 40% had received the drug for >3 years. BCR-ABL mutations were present at baseline in 45% of patients randomized to receive dasatinib (n = 101) and 22% of those in the imatinib (n = 49) arm.

- At a median follow-up of 15.2 months in the START-C trial, major and complete cytogenetic responses occurred in 59% and 49% of dasatinib recipients with chronic phase CML with imatinib resistance or intolerance (figure 2).

- For both of these endpoints, the rate of response was numerically higher among imatinib-intolerant than imatinib-resistant patients. Major and complete cytogenetic responses were evident in 80% and 75% of imatinib-intolerant patients, respectively, compared with 52% and 40% of imatinib-resistant patients. The durability of the cytogenetic response was confirmed, in that 97% of patients who had achieved a major cytogenetic response had no evidence of subsequent disease progression.

- A major cytogenetic response was achieved with dasatinib in imatinib-resistant or -intolerant patients, irrespective of the presence of BCR-ABL mutations. The major cytogenetic response rate was 59% in patients with a BCR-ABL mutation.

- Progression-free survival with dasatinib at 15 months in the START-C trial was 90% and overall survival was 96%.
Keam

Cytogenetic responses in patients with a high degree of resistance to imatinib were also significantly more frequent with dasatinib than high-dose imatinib. Response rates were 7-fold higher in those with no previous cytogenetic response to imatinib (49% vs 7%; p = 0.006) and 2-fold higher in those who had previously not responded to imatinib 600 mg/day (49% vs 24%; p = 0.015).

Treatment failure was less likely with dasatinib than high-dose imatinib in imatinib-resistant patients with chronic phase CML. The median time to treatment failure with dasatinib had not been reached after a median follow-up of 15 months, but was 3.5 months with high-dose imatinib (hazard ratio for the between-group difference 0.16; 95% CI 0.1, 0.26) [p < 0.001]. Progression-free survival was also more likely with dasatinib than high-dose imatinib (hazard ratio 0.14; 95% CI 0.05, 0.4) [p < 0.001].

A complete hematologic response was evident in significantly more dasatinib than high-dose imatinib recipients in the START-R trial (93% vs 82%; p = 0.034).

The START-A trial (CA 180005) enrolled 174 patients with Ph-positive (or BCR-ABL positive) accelerated phase CML and progression was defined by any one of the following: development of accelerated or blast phase disease, loss of major cytogenetic response, loss of complete hematologic response or an increasing white blood cell count.

- A complete hematologic response was seen in 91% of dasatinib recipients after a median 15.2 months’ follow-up in the START-C trial.
- In the START-R trial, the median duration of therapy with dasatinib was 13.7 months and that with high-dose imatinib (800 mg/day) was 3.1 months; those remaining on the initially allocated treatment received a median 13–14 months of treatment with either drug.

At a median follow-up of 15 months, significantly fewer patients had discontinued dasatinib than high-dose imatinib (28% vs 81%; p < 0.0001). The most common reason for discontinuing treatment was lack of response or disease progression (61% of imatinib and 5% of dasatinib recipients) or drug intolerance (18% of imatinib and 16% of dasatinib recipients).

Dasatinib therapy achieved significantly greater major and complete cytogenetic responses than high-dose imatinib in patients with imatinib-resistant chronic phase CML in the START-R trial. At a median follow-up of 15 months, major (52% vs 33%; p = 0.023) and complete (40% vs 16%; p = 0.004) cytogenetic responses were significantly greater with dasatinib than high-dose imatinib.

- Cytogenetic responses in patients with a high degree of resistance to imatinib were also significantly more frequent with dasatinib than high-dose imatinib. Response rates were 7-fold higher in those with no previous cytogenetic response to imatinib (49% vs 7%; p = 0.006) and 2-fold higher in those who had previously not responded to imatinib 600 mg/day (49% vs 24%; p = 0.015).

- Treatment failure was less likely with dasatinib than high-dose imatinib in imatinib-resistant patients with chronic phase CML. The median time to treatment failure with dasatinib had not been reached after a median follow-up of 15 months, but was 3.5 months with high-dose imatinib (hazard ratio for the between-group difference 0.16; 95% CI 0.1, 0.26) [p < 0.001]. Progression-free survival was also more likely with dasatinib than high-dose imatinib (hazard ratio 0.14; 95% CI 0.05, 0.4) [p < 0.001].

- A complete hematologic response was evident in significantly more dasatinib than high-dose imatinib recipients in the START-R trial (93% vs 82%; p = 0.034).

Accelerated Phase CML (START-A)

The START-A trial (CA 180005) enrolled 174 patients with Ph-positive (or BCR-ABL positive) accelerated phase CML and imatinib resistance or intolerance. Follow-up data (107 evaluable patients) at 8 months have been published. However, this review focuses on the more recent follow-up data at a minimum of 9 months’ follow-up and a median 14.1 months for the full cohort of 174 patients (available as abstracts).

The median time from initial diagnosis of CML was 82 months. Patients had previously been treated with interferon-α (72%), stem-cell transplantation (13%), imatinib >600 mg/day (52%) and/or imatinib for a duration >3 years (59%). After a minimum of 9 months’ follow-up, a major hematologic response (primary endpoint; figure 3) was seen in 63% of patients (consisting of complete hematologic response in 43% of patients and no evidence of leukemia in 20% of patients). In addition, major hematologic responses occurred in 69% of the 94 patients with BCR-ABL mutations at baseline.

Hematologic responses were durable; for instance, after a minimum of 9 months’ follow-up, a major hematologic response was maintained in 85% of patients.

At a median 14.1 months’ follow-up, a complete hematologic response was evident in 45% of patients. A major cytogenetic response was seen in 39% of patients, with a complete cytogenetic response in 32% of patients (figure 2). Estimated 12-month progression-free survival was 66% and estimated 12-month overall survival was 82%.
In the START-B (CA 180006) and START-L (CA 180015) trials,[42,47] 109 patients with myeloid blast phase CML (START-B) and 48 patients with lymphoid blast phase CML (START-L) with imatinib resistance or intolerance were treated with dasatinib. Follow-up data at 8 months for 116 evaluable patients have been published.[42] However, this review focuses on longer-term follow-up data (minimum 12 months) for the full patient cohort (available as an abstract).[47]

In the 157 patients with myeloid or lymphoid blast phase CML enrolled in the START-B or -L trials, the median time from initial diagnosis of CML was 44 months.[47] Prior treatment included stem-cell transplantation (19%) and imatinib (dosage >600 mg/day in 50% of patients and duration >3 years in 36%).[47]

- Major hematologic response occurred in 34% of CML patients in myeloid blast phase (START-B) and 35% of patients in lymphoid blast phase (START-L),[47] with complete hematologic response in 27% and 29% of patients[11] (figure 3).
- Major cytogenetic response occurred in 33% of patients with myeloid blast phase CML, with complete cytogenetic response in 26% of patients (figure 2).[47] In patients with lymphoid blast phase CML, the major cytogenetic response rate was 52%, with a complete cytogenetic response in 46% of patients (figure 2).[47]
- Median progression-free survival was 6.7 months in patients with myeloid blast phase CML and 3.0 months in those with lymphoid blast phase CML. The respective median overall survival durations were 11.8 and 5.3 months.[47]

**Phase III Dose-Optimization Trials**

In the trial in adult patients with chronic phase CML who were resistant to or intolerant of imatinib, 670 patients were randomized to dasatinib 100 mg once daily ($n = 167$), 50 mg twice daily ($n = 168$), 140 mg once daily ($n = 167$) or 70 mg twice daily ($n = 168$).[25] Results reported are after a median duration of treatment of 8 months (range <1 to 15 months).[43] The median time from CML diagnosis to trial entry was 54 months.[43] Approximately 40% of these patients had previously received imatinib therapy for >3 years, and 34% had received high-dose (>600 mg/day) imatinib and 74% were imatinib resistant.[46] The noninferiority of a once-daily versus a twice-daily dasatinib regimen was established if the lower bound of the 2-sided 95% confidence interval of the difference between the major cytogenetic response rates with the two regimens was above -15%.[45]

- Once- or twice-daily dasatinib regimens were similarly effective in patients with chronic phase CML who were resistant to or intolerant of imatinib.[25,43] At a median of 8 months’ follow-up, combined results for each dosage regimen showed that a major cytogenetic response was seen in 52% of those receiving the drug once daily and 49% of those receiving a twice-daily regimen (primary endpoint).[45] The between-group difference was 2.8% (95% CI -6.0, 11.6).[25]
- Major cytogenetic response rates in the individual treatment arms were 59% and 56% with the 100 mg and 140 mg once-daily

![Graph showing hematologic response rates](image-url)
dosages and 54% and 55% with the 50 mg and 70 mg twice-daily dosages.\[25\]

- In addition, there was no difference in efficacy between the dasatinib 100 mg and 140 mg total daily dosages (between-group difference \(-0.8\%\); 95% CI \(-9.6, 8.0\)).\[25\] A dasatinib 100 mg once-daily regimen is considered the optimal dosage in imatinib-resistant or -intolerant patients with chronic phase CML (section 5).

- Complete cytogenetic response rates did not differ between dosage regimens (41–45%).\[25\] nor did the durations of major cytogenetic responses or progression-free survival.\[24,43\] Complete hematologic responses were evident in 86–92% of patients.\[25\]

In the trial in imatinib-resistant or -intolerant patients with advanced phase (accelerated phase, myeloid blast phase or lymphoid blast phase) CML or Ph-positive ALL, 611 patients were randomized to receive dasatinib 140 once daily or 70 mg twice daily.\[44,45\] Results are at a median of \(\approx 6\) months’ follow-up (range <1 to 16 months).\[44,45\] The median time from CML diagnosis to trial entry was 58 months.\[45\] More than one-third of these patients had previously received imatinib therapy for \(>3\) years, 43% had received high-dose (>600 mg/day) imatinib and 78% were imatinib resistant.\[44,45\] Noninferiority of the once-daily to the twice-daily regimen was established if the lower bound of the 2-sided 95% confidence interval of the difference between the major hematologic response rates with the two regimens was at or above \(-12\\%\).\[45\]

- Major hematologic response rates (primary endpoint) at a median follow-up of \(\approx 6\) months not differ between once-daily or twice-daily dasatinib regimens in imatinib-resistant or -intolerant patients with advanced phase (accelerated phase, myeloid blast phase or lymphoid blast phase) CML or Ph-positive ALL (48% vs 48%) [between-group difference 0.2%; 95% CI \(-7.8, 8.1\)].\[25,45\]

- The median duration of major hematologic response was 10.2 months with once-daily dasatinib compared with 12.3 months with the twice-daily regimen, and median durations of progression-free survival with the respective regimens were 7.9 versus 11.7 months.\[44\] Additional analysis showed that twice as many patients receiving once-daily dasatinib compared with the twice-daily regimen relapsed after achieving a hematologic response (30% vs 16%).\[45\]

- Most relapses occurred in patients with lymphoid blast phase CML (77% with once-daily dasatinib vs 11% with the twice-daily regimen) or Ph-positive ALL (87% vs 43%).\[45\] In patients with accelerated phase CML, the corresponding relapse rates were 13% and 10%, and those in patients with myeloid blast phase CML were 40% and 32%.\[45\] Dasatinib 70 mg twice daily remains the recommended regimen in imatinib-resistant or -intolerant patients with accelerated phase, myeloid blast phase or lymphoid blast phase CML or Ph-positive ALL (section 5).\[25\]

### 4. Tolerability

The tolerability of dasatinib in patients with CML and Ph-positive ALL has been investigated in phase I and phase II trials, and two phase III dose-optimization trials (see section 3). Pooled tolerability data in dasatinib-treated patients \((n = 2182)\) enrolled in these clinical trials have been reported in the European prescribing information. The median duration of dasatinib therapy was 7 months (range 0–19 months) and starting dosages were 100 mg once daily, or 50 or 70 mg twice daily.\[25\] Older patients were well represented in clinical trials; 23% of patients were aged \(>65\) years and 4% were aged \(>75\) years.\[25\] This section focuses on the pooled data,\[25\] supplemented by data from individual trials\[43,44\] and case reports,\[54–56\] where required.

- Adverse events were reported in the majority of patients treated with dasatinib during clinical trials.\[25,45\] According to the pooled data, adverse events were generally mild to moderate in severity, with the most commonly reported adverse events (incidence of 12–29%) being fluid retention events (including superficial edema or pleural effusion), gastrointestinal adverse events (including diarrhea and nausea), skin rash, headache, hemorrhage, musculoskeletal pain, dyspnea, pyrexia and fatigue.\[25\]

- A minority of patients discontinued treatment because of adverse drug reactions (6% with chronic phase CML, 9% with accelerated phase CML, 13% with myeloid blast phase CML and 5% with lymphoid blast phase CML or Ph-positive ALL).\[25\] In patients with chronic phase CML, treatment discontinuation because of adverse events in the phase III dose-optimization trial was 3% with dasatinib 100 mg once daily and 11% with dasatinib 70 mg twice daily.\[25\]

- Most patients with chronic phase CML who were intolerant of imatinib tolerated dasatinib therapy.\[25\]

- The most common grade 3/4 (severe/life-threatening or disabling) nonhematologic adverse events included fluid retention in 6% of patients (pleural effusion [4%], pulmonary edema [1%], pericardial effusion with or without superficial edema [1%], ascites [<1%], and generalized edema [<1%]) and hemorrhage, also in 6% of patients (4% gastrointestinal and 2% other bleeding). Individual grade 3/4 nonhematologic adverse events of interest reported in >1% of dasatinib-treated patients are shown in figure 4.\[25\] Drug-related febrile neutropenia was reported in 5% of dasatinib recipients.\[25\]

- Most grade 3/4 bleeding events were associated with grade 3/4 thrombocytopenia; grade 3/4 CNS hemorrhage was uncommon (<1%) in clinical trials, but resulted in seven deaths.\[25\]

- Grade 3/4 thrombocytopenia (71–81% of patients), grade 3/4 neutropenia (66–79%) and grade 3/4 anemia (53–73%) were more common in patients with accelerated phase, myeloid blast phase or lymphoid blast phase CML or Ph-positive ALL than in patients with chronic phase CML (incidences of these grade 3/4 cytopenias being <1%).
Thereafter, treatment can be resumed as appropriate at a reduced dose depending upon the initial severity of the event.[25]

- Of interest, dasatinib-induced pleural effusions were not correlated with generalized fluid retention, were usually exudates and often responded to corticosteroid therapy, suggesting that they may be mediated by immune mechanisms, including PDGFR-β.[54,56]

- Dasatinib therapy was associated with QT interval prolongation in only a minority of patients.[25] The QT interval corrected for heart rate by Fridericia’s method (QTcF) was prolonged in 9 of 467 patients receiving dasatinib 70 mg twice daily in the five phase II trials and three patients had evidence of a QTcF interval >500 msec. Heart rate, and PR or QRS interval were unaffected. Caution is required when dasatinib is administered in patients with evidence of or potential for QT prolongation.[25]

5. Dosage and Administration

Dasatinib is indicated for the treatment of adults with chronic phase or advanced phase (accelerated, myeloid blast or lymphoid blast phase) CML and resistance to or intolerance of prior therapy (including imatinib).[25] Dasatinib is also indicated for the treatment of adults with Ph-positive ALL and lymphoid blast CML and resistance or intolerance of prior therapy.[25] The recommended starting dosage of dasatinib for imatinib-resistant or -intolerant patients with chronic phase CML is 100 mg once daily (either morning or evening at the same time each day), while that in imatinib-resistant or -intolerant patients with accelerated, myeloid or lymphoid blast phase CML or Ph-Positive ALL is 70 mg twice daily (once in the morning and once in the evening) with or without food. In clinical studies, dose escalation was permitted in patients who did not achieve a hematologic response or cytogenetic response at the recommended dosage (to 140 mg once daily in patients with chronic phase CML or to 100 mg twice daily in patients with advanced phase CML or Ph-positive ALL). Dose increases or reductions in 20 mg increments are recommended based on individual tolerability. In clinical studies, treatment with dasatinib was continued until disease progression or until dasatinib was no longer tolerated.[25]

The effect of stopping treatment in patients who have achieved a complete cytogenetic response has not been investigated.[25]

Local prescribing information should be consulted for detailed information, including dose adjustments in the event of myelosuppression, special warnings and precautions, and contraindications.

6. Dasatinib: Current Status

Dasatinib is a multiple tyrosine-kinase inhibitor that is effective against most imatinib-resistant isoforms of BCR-ABL. Based on its efficacy and tolerability in clinical trials (sections 3 and 4), this agent is approved for use in Europe[25] and elsewhere (including
the US[52]) for the treatment of patients with chronic, accelerated, or myeloid or lymphoid blast phase CML and resistance to or intolerance of prior therapy (including imatinib). This agent is also approved for use in therapy-resistant or -intolerant patients with Ph-positive ALL. The use of dasatinib in these patient populations has now been recommended in updated US treatment guidelines,[1] European guidelines[5] have not yet been updated.

Historically, patients with chronic phase CML and resistance to or intolerance of prior therapy have had limited treatment options. For such patients, dasatinib is the first approved treatment. More than half of those treated in a phase II trial achieved a major cytogenetic response (section 3).

Major cytogenetic response rates in imatinib-resistant patients with more advanced CML were generally lower than those in the patients with chronic phase disease; nevertheless, based on major hematologic response rates, dasatinib represents an option for these difficult-to-treat patients (section 3). In the phase II START-R trial in imatinib-resistant patients with chronic phase CML, dasatinib 70 mg twice daily improved cytogenetic response rates and progression-free survival to a greater extent than high-dose imatinib (800 mg/day).[38]

A once-daily treatment regimen with a starting dosage of dasatinib 100 mg is now recommended in imatinib-resistant or -intolerant patients with chronic phase CML, based on results of phase III dose-optimization trials in which a once-daily dasatinib regimen was as effective, but better tolerated, than a twice-daily regimen.[25,43] However, a twice-daily dasatinib 70 mg dosage regimen continues to be recommended in patients with accelerated, or myeloid or lymphoid blast phase CML or Ph-positive ALL with resistance to or intolerance of prior therapy (including imatinib).[25,44] Numerous studies of dasatinib in imatinib-resistant or -intolerant patients with CML or Ph-positive ALL are ongoing.

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