

Efficacy of dasatinib for the treatment of intractable chronic myeloid leukemia

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Abstract: Dasatinib (DAS) is a well tolerated oral dual SRC inhibitor with remarkable activity against all phases of imatinib-resistant chronic myeloid leukemia (CML). This paper focuses on the activity of DAS in intractable CML, and reviews outcomes of patients enrolled on DAS clinical trials. Safety and tolerability as well as practical tips for management of side-effects, and drug interactions are included.

Keywords: dasatinib, resistant CML, outcomes

Introduction

Chronic myeloid leukemia (CML) is a clonal stem cell proliferative disorder,¹ characterized by a well-recognized triphasic clinical course and by the presence of a hybrid oncogene, the BCR-ABL. CML patients often present during the indolent phase of the disease or chronic phase (CP), and evolve, in the absence of effective treatment, to a more resistant (accelerated phase [AP]) and rapidly fatal terminal phase (blast phase [BP]).² Historically, progression to blast phase was observed in 5% during the first year after diagnosis, 15% in the second year and then at a rate of 25% per year thereafter. BCR-ABL, the hallmark of CML, is the result of a reciprocal translocation between chromosome 9 and 22 (the Philadelphia chromosome, or Ph+) which juxtaposes two genes intimately engaged in cell signaling, signal transduction and cell proliferation.^{2,3} The ABL gene specifically encodes for nonreceptor tyrosine kinases, whose tightly controlled physiologic activities become deregulated and constitutively active by the juxtaposition of BCR. Additionally, BCR-ABL plays a central role in controlling downstream pathways involved in cell proliferation, regulation of cellular adhesion and apoptosis. With the observation that transduction of murine stem cells with retroviral vectors containing the chimeric BCR-ABL fusion gene caused in mice a disease closely resembling human CML,⁴ targeting BCR-ABL has become the mainstay of modern therapy in CML.

Targeting BCR-ABL in CML

The introduction of specifically designed inhibitors of BCR-ABL tyrosine kinase activity has dramatically improved outcomes of CML. In 2010, patients with newly diagnosed CP-CML treated with the tyrosine kinase inhibitor (TKI) imatinib mesylate ([IM], GLEEVEC[®]; Novartis, East Hanover, NJ) can expect excellent chances of durable complete hematological ([CHR], >98%), complete cytogenetic ([CCyR], >80%), and major molecular responses ([MMR], >50%). These spectacular responses did translate

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into improved 5–7 years disease-free (DFS) and overall (OS) survivals (83% and 90%, respectively).^{5,6}

Resistance to IM

Despite the impressive results observed with IM, primary and secondary resistances to IM occur. The annual failure rate on IM is 3% during the first year, doubles (7%) during the second, and decreases in the third year (5%) and beyond.⁵ However, statistics on subsequent failure rates are marred by patient selection biases on a trial that has lost more than 40% of accrued patients to follow-up once IM became commercially available.⁵ Additionally, up to 15% of patients fail to achieve a major cytogenetic response 12 months after starting IM, which increases the risk of disease progression in the ensuing years.^{5,6} Resistance to IM is multifactorial and can in 50% of the cases be explained by the detection of acquired ABL kinase domain point mutations.⁷ These point mutations lead to stereotactic distortions of BCR-ABL that prevent IM from binding to its high-affinity binding site. To overcome these resistances, second generation tyrosine kinase inhibitors were developed, some with enhanced binding affinity (nilotinib, Tasigna®; Novartis)^{8,9} others with binding affinity to the catalytically active state of the tyrosine kinase (dasatinib, Sprycel®, Bristol Myers Squibb, New York, NY, USA; bosutinib,¹⁰ SKI-606, Pfizer, NY).

Dasatinib

Dasatinib (DAS) is an orally bioavailable dual SRC-ABL inhibitor with very potent activity against BCR-ABL, the family of SRC kinases, ephrin receptor kinases, platelet-derived growth factor receptor (PDGFR), cKit, as well as other tyrosine and tyrosine/threonine kinases.¹¹ DAS binds predominantly to the ATP-binding site and to the active conformations of BCR-ABL.^{11,12} DAS's independence from key residues essential for IM activity translates into improved activity against most mutations that confer resistance to IM, with the exception of T315I.^{12,13} DAS's activity against IM-resistant BCR-ABL+ cells was demonstrated both *in vitro* and in a mouse model of IM-resistant BCR-ABL-dependent disease.¹³ DAS inhibits phosphorylation of the BCR-ABL substrate CRKL in all BCR-ABL mutant cell lines with the exception of T315I. Certain mutations, specifically the F317L, did require higher concentrations of DAS to inhibit phosphorylation of CRKL. When severe combined immunodeficient mice injected with Ba/F3 cells expressing BCR-ABL isoforms and the firefly luciferase gene, a decrease in tumor burden measured by bioluminescence imaging was observed in DAS-treated mice harboring the wild-type

BCR-ABL and M351T, but not the T315I mutant.¹³ These experiments laid the ground for a first in human clinical trial. In a Phase I trial, IM-resistant CML and Ph+ acute lymphoblastic leukemia were enrolled on cohorts testing increasing doses of DAS, initially once daily, and as pharmacokinetic data became available, on a twice a day schedule.¹⁴ Similar to what was observed with IM, DAS was well-tolerated, and a maximum tolerated dose was not reached. The half-life of DAS is 3–5 hours. At doses ≥ 50 mg/d, approximately 40% of patients had evidence of hematologic or cytogenetic responses.^{14,15} The dose schedule of 70 mg twice a day was subsequently selected for phase II trials.

Treatment of IM-resistant CP-CML with DAS

With DAS administered at 70 mg twice daily, 90% of CP CML with acquired resistance to IM achieve CHR within 15 days. So far and with 2 years follow-up, major and CCyR are observed in 40%–50%, with progression-free and overall survivals of >90% (Table 1).^{16,18} DAS is also active in CP CML with primary resistance to IM. Indeed, for CP CML patients with no CHR after 3 months, no cytogenetic response after 6 months, or no major cytogenetic response after 12 months of IM 400 mg/d, a switch to DAS (70 mg twice daily) is associated with higher CCyR (40% vs 16%) and MMR (16% vs 4%) as compared to a dose-escalation of IM to 800 mg/d.^{19,20} The dose schedule of 70 mg twice-daily was re-evaluated after maturing data from the phase I study showed that BCR-ABL kinase inhibition was more sustained across a 24-hour period with the once-daily schedule. This observation led to a large dose-optimization trial that randomized IM-resistant CP-CML patients to a four dose schedules of DAS: 70 mg twice daily, 50 mg twice daily, 140 mg once daily, and 100 mg once daily.^{18,21} Consistent hematologic and cytogenetic responses were observed across all dose-schedule/total daily dose arms: CHR 85%–90%; major cytogenetic responses, 55%–60%; CCyR, 40%–45%.^{18,21} Interestingly, patients who received the 100 mg once daily dose experienced fewer adverse events (AEs) and required fewer dose interruptions. The more favorable safety profile combined with equivalent activity led to a change in the label of the approved dose for DAS in patients with CML-CP to 100 mg once daily.

Treatment of IM-resistant advanced phases CML with DAS

DAS is a very active agent in advanced phases of CML (Table 1).^{15,22–24} More than 75% of IM-resistant AP patients

Table 1 Outcomes associated with treatment of IM-resistant CML with DAS according to phase of CML

CML phase	CHR	MCyR/CCyR	MMR	Median follow up	PFS	OS
Chronic phase ¹⁶⁻²¹	91%–93%	53%–63%/50%–53%	37%–47%	24 mo	80%–86%	91%–94%
Accelerated phase ²²⁻²³	45%–52%	39%–43%/32%–33%	n/a	15 mo	66%	78%–82%
Blast phase ²⁴	25%–29%	33%–52%/26%–46%	n/a	12 mo	3–7 mo	5–12 mo

Abbreviations: CML, chronic myeloid leukemia; CHR, complete hematological remission; MCyR, major cytogenetic remission; CCyR, complete cytogenetic remission; MMR, major molecular response; PFS, progression-free survival; OS, overall survival.

treated with DAS 70 mg twice daily achieve a hematologic response, of which approximately half are complete. Additionally, up to 40% of those patients also achieve a major cytogenetic response, a third of which are complete. Responses are durable with a median 1 and 2 years progression-free survival (PFS) of 68% and 52%, and overall survival (OS) of 80% and 70%, respectively.^{22,23} Initial responses with DAS in IM-resistant BP patients are also quite impressive, but short-lived. Indeed, 50% of patients achieve a hematologic response and 30%–50% a major cytogenetic response.²⁴ However, PFS is only 3–6 months, and consequently OS approximates 12 months. As compared to CP CML, higher doses of DAS are required for advanced phases and no improvements in responses were observed when the dose of 140 mg was administered once a day or in two divided doses (70 mg twice daily). However, the once a day regimen demonstrated a safer toxicity profile and fewer dose reductions and interruptions.²³

Managing side effects of DAS

DAS is overall well tolerated. Treatment-related AEs usually occur early, are reversible, and lead to discontinuation of DAS in 8%–16% in patients with CP-CML, and 4%–10% in AP and BP patients.²⁵ Hematologic AEs are common in all phases of CML, but occur more frequently in the advanced phases. DAS-induced cytopenias occur in the first 3 months of therapy, resolve 2–3 weeks after DAS is held, and are usually managed with standard supportive care (prophylactic antibiotics, transfusions), treatment interruption, and/or dose reduction. Despite the high incidence of cytopenias, neutropenic fevers are uncommon (<5%). In patients with advanced disease, where up to 80% of patients develop pancytopenia, a bone marrow biopsy can help differentiate DAS-induced cytopenia (ie, hypoplastic or aplastic bone marrow) from cytopenia caused by leukemic marrow infiltration (hypercellular marrow with persistent blasts). Erythropoietin administration is not approved by the United States Food and Drug Administration in the setting of DAS-associated anemia. Thrombocytopenia (platelet level <50 × 10⁹/L) is less common in CP-CML with the

100 mg once daily regimen (20% versus 45% with the 70 mg twice daily),^{17,21} but can be observed in up to 80% of patients with advanced phases.^{15,22–24} Nevertheless, bleeding is relatively rare occurring in <5%.²⁵ DAS-associated platelet dysfunction,²⁶ may explain the occasional bleeding events that occur in the absence of thrombocytopenia. The most common nonhematologic AEs are gastrointestinal toxicities, headaches, fatigue, peripheral edema, and pleural effusions.^{16,17,19,21–24} Nausea, vomiting, and diarrhea are usually mild (grade 1/2) occurring in up to 25% of patients, and are manageable with supportive care agents.²⁵ Although antacids and proton pump inhibitors are commonly used to alleviate nausea in cancer patients, these drugs should be avoided in DAS-treated patients as the solubility of DAS is pH dependent.²⁷ Headaches and fatigue often improve with holding and restarting the drug at a lower dose, and do not necessarily recur with attempts to re-escalate the dose of DAS. Pleural effusions are observed in up to 10% of patients treated with DAS.²⁸ The timing of onset of these exudative effusions appears to be dose and schedule-dependent: late (73 weeks) with the once daily 100 mg dose and early (4 weeks) in patients treated with 140 mg daily.^{21,29} Pleural effusions lead to discontinuation of DAS in 6%.²⁸ Mechanisms that lead to development of pleural effusion are not well understood and remain largely speculative.²⁸ DAS targets pathways involved in regulation of tissue interstitial fluid pressure (PDGFR-b),^{29,30} and permeability of pleural/pulmonary vasculature (SRC, YES) which may explain the occurrence of these effusions.^{29,31,32} Multivariate analyses have identified patients at risk for the development of pleural effusions on DAS therapy. These factors include older age, hypertension, prior cardiac history, a twice daily dose schedule, and to a certain degree, advanced phases of the disease.^{29,30} Pleural effusions should be suspected when patients present with dry cough, chest tightness, or shortness of breath. Given the lack of understanding of the underlying pathophysiology of DAS-induced pleural effusions, the management remains supportive and includes dose interruption/reduction, diuretics, low-dose corticosteroids, and thoracentesis for symptomatic/severe effusions.²⁹

Drug interactions

Absorption of DAS is not affected by food.²⁷ DAS solubility is pH dependent, therefore caution should be used with antacids, and proton pump inhibitors should be avoided during treatment with DAS. Dasatinib is a substrate for CYP3A4, therefore other CYP3A4 substrates, inducers, or inhibitors will interfere with the metabolism of DAS.²⁷ CYP3A4 substrates and specifically those with a narrow therapeutic index such as cyclosporine and fentanyl simvastatin,²⁵ may see their concentration competitively altered by the concurrent administration of DAS and should therefore be carefully monitored for specific toxicities and dose adjusted accordingly. CYP3A4 inducers such as with rifampicin, dexamethasone, St John's Wort, phenytoin, and phenobarbital can decrease the blood concentration of DAS up to 80%.^{15,25,33} Finally, CYP3A4 inhibitors, such as ketoconazole, macrolide antibiotics, azole antifungals, and grapefruit juice can increase the toxicity of DAS through an increase in plasma concentration. The use of anticoagulants or platelet inhibitors are not contraindicated, however, given the risk for platelet dysfunction during treatment with DAS, these drugs should be used with extreme caution.

Future directions

Outcomes of CML patients have improved remarkably with the use of targeted therapy, and for patients with disease resistant to IM, excellent responses with second line agents such as DAS can be achieved. The follow-up of DAS-treated patients remains relatively short, and longer follow-up will shed more light on the durability of these responses. The activity of DAS is maintained despite the presence of mutations that confer resistance to IM with the exception of the T315I mutation, and to a large degree, mutations affecting the residue 317 (F317L, F317V).³⁴ The V299L mutation, although rarely acquired on IM, is often detected at the time of DAS failure.³⁵ For those patients with the 299 and 317 mutations detected at the time of initiation of DAS, other agents such as nilotinib, bosutinib (SKI606; Pfizer, New York, NY), or other drugs in development (INNO-406, AP24534), if available, should be considered.³⁴ Alternatively, and with the exception of the T315I mutation, DAS can be successfully used as a stepping stone for allogeneic stem cell transplantation. The outcomes of patients allografted after exposure to second-line tyrosine kinase inhibitors are currently being analyzed in an ongoing European Bone Marrow Transplant registry study.³⁶ Preliminary results have shown that, similar to IM,³⁷ disease status at conditioning, rather than pretransplant treatment with DAS, dictates

outcomes of transplantation. Finally, and for patients with no suitable donor or who are not eligible for transplantation, better understanding of the effects of DAS on the immune system may offer hopeful future alternatives. Indeed, recently a quite fascinating report described the development of clonal lymphoproliferative disorder characterized by the presence of large granular natural killer/T-lymphocytes in DAS-treated patients.³⁸ Although a higher rate of autoimmune complications (pleurisy, colitis) were observed in these patients with clonal lymphocytic expansion, responses to DAS were excellent, especially for advanced phase patients, and unexpectedly long-lasting. Indeed, all IM-resistant or intolerant Ph+ acute lymphoblastic leukemia who developed chronic lymphocytosis after treatment with single agent DAS were alive 2 years after starting DAS, and 66% were still in remission. In contrast, median DFS and OS for patients without lymphocytosis were dismal, 2.7 and 5.8 months, respectively. Elucidating pathways that lead to this immune phenomenon would add an extremely potent antileukemic intervention to the armamentarium against CML.

Disclosure

The authors report no conflict of interest in this work.

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