

BC Cancer Protocol Summary for Treatment of Chronic Myeloid Leukemia and Ph+ Acute Lymphoblastic Leukemia using daSATinib

Protocol Code

LKCMLD

Tumour Group

Leukemia

Contact Physician

Dr. Donna Forrest

ELIGIBILITY:¹⁻²

- Patients with **chronic phase CML**, who are resistant to iMAtinib:
 - No complete hematologic response (CHR) after 3 months of iMAtinib
 - Lack of any cytogenetic response after 3 months of iMAtinib
 - Lack of major cytogenetic response (MCR/1 log reduction bcr-abl) after 6 months of iMAtinib
 - Lack of complete cytogenetic response (CCR/2 log reduction bcr-abl) after 12 months of iMAtinib
 - Cytogenetic relapse on iMAtinib (loss of CCR/less than 2 log or MCR/less than 1 log or any Ph+ increase greater than or equal to 30%)
 - Loss of CHR
 - Progression to accelerated or blast phase CML
- Patients with **accelerated/blast phase CML, including Ph+ acute lymphoblastic leukemia (ALL) patients**, who are resistant to iMAtinib:
 - Lack of response following greater than or equal to 4 weeks of treatment with iMAtinib greater than or equal to 600 mg PO once daily
 - No CHR in accelerated phase (AP) after 3 months of iMAtinib use
 - Incomplete response with no further improvement in blast phase/Ph+ ALL after 1 month of iMAtinib greater than or equal to 600 mg PO once daily
 - Cytogenetic relapse (loss of CCR/less than 2 log or MCR/less than 1 log or any Ph+ increase greater than or equal to 30%)
 - Loss of CHR
 - Progression of AP to blast phase or recurrent blast phase/Ph+ ALL
- Patients with **chronic/accelerated/blast phase CML, including Ph+ ALL patients**, who are **intolerant** to iMAtinib, including patients with:
 - greater than or equal to Grade 3 non-hematologic toxicity, not responding to symptomatic treatment or dose adjustments to iMAtinib 300 mg PO once daily
 - Grade 4 hematologic toxicity lasting greater than 7 days
 - Sustained, highly symptomatic Grade 2 non-hematologic toxicity
 - Patients with intolerance to niLOtinib (grade 3 or 4 non-hematologic toxicity) for chronic/accelerated phase CML treatment. Note: sequential use between daSATinib and niLOtinib for disease progression is not allowed unless a specific kinase domain mutation is demonstrated mediating resistance to one second generation TKI but has demonstrated sensitivity to the other TKI.
- May be used in combination with busulfan, dexamethasone, hydroxyUREA, interferon, melphalan or predniSONE

EXCLUSIONS:¹⁻²

- Patients with hypersensitivity to daSATinib or to any other components of the drug.
- Additional caution should be used in patients:
 - who are at risk for QTc interval prolongation, based on their baseline ECG, medical conditions such as thiamine deficiency, or use of medications that may predispose them to QTc interval prolongation, such as amiodarone, arsenic, chloroquine, chlorpromazine, clarithromycin, disopyramide, domperidone, droperidol, erythromycin, haloperidol, ibutilide, methadone, MOXifloxacin, pentamidine, pimozide, procainamide, quinine, quinidine, sotalol, and so on.
 - who are at an increased risk for bleeding, including those receiving anticoagulant medications such as low molecular weight heparin, unfractionated heparin, warfarin, or antiplatelet therapy such as abciximab, ASA, clopidogrel, dipyridamole, eptifibatide, ticlopidine, etc.

TESTS:¹⁻²

- Baseline: CBC and diff., platelets, **ALT**, bilirubin, serum creatinine, BUN, body weight, bone marrow examination for cytogenetic analysis, FISH, RT-PCR (for BCR/ABL transcripts) and ECG.
- **Baseline:** (required, but results do not have to be available to proceed with first treatment; results must be checked before proceeding with cycle 2): HBsAg, HBcoreAb
- *Monitoring for disease progression*
(www.healthcareprofessionals.leukemiabmtprogram.com/CMG/CML/Treatment.aspx)
 - CBC & diff, platelets: weekly until **CHR** then monthly; after 6 months and if patient is clinically stable, may increase interval to every 3 months at the physician's discretion
 - Serum creatinine, uric acid, **ALT**, bilirubin: weekly until stable then monthly; after 6 months and if patient is clinically stable, may increase interval to every 3 months at the physician's discretion
 - Peripheral blood QPCR (for BCR/ABL transcripts): every 3 months until **MMR** achieved and maintained for at least 12 months, then QPCR (for BCR/ABL transcripts) is measured every 6 months
 - Bone marrow aspirate and biopsy: at diagnosis, then as clinically indicated
- *Monitoring for dose modifications:* CBC & diff, Platelets, **ALT**, Bilirubin
 - first month: every 1-2 weeks (physician will be responsible to check and advise patient on dose adjustment)
 - months 2-6: every month
 - after 6 months: every 3 months
- ECG should be repeated seven days after start of treatment and as clinically indicated, including seven days after dose changes

PREMEDICATIONS:

- Antiemetic protocol for low emetogenic chemotherapy protocols (see SCNAUSEA).

SUPPORTIVE MEDICATIONS:

- If HBsAg or HBcoreAb positive, start lamivudine 100 mg/day PO for the duration of chemotherapy and for six months afterwards.

TREATMENT:²

Drug	Disease	Dose	BC Cancer Administration Guideline
daSATinib	CML chronic phase	100 mg once daily	PO
	CML accelerated phase	140 mg once daily	
	CML blast phase		
	Ph+ acute leukemias		

DOSE MODIFICATIONS:**1. Hematological:²****Chronic Phase:**

ANC (x10 ⁹ /L)	Dose (PO)
greater than or equal to 1.0	100%
less than 1.0	Hold until ANC greater than or equal to 1.0: <ul style="list-style-type: none"> • 1st episode: <ul style="list-style-type: none"> ○ greater than or equal to 1.0 in less than or equal to 7 days: daSATinib 100 mg once daily ○ greater than or equal to 1.0 in greater than 7 days: daSATinib 80 mg once daily • 2nd episode: <ul style="list-style-type: none"> ○ greater than 7 days: Physician to determine how to proceed • Febrile neutropenia with or without signs and symptoms of sepsis: <ul style="list-style-type: none"> ○ 1st episode: discharge daSATinib until ANC greater than 1.0 and T less than 38 °C, then resume daSATinib 80 mg once daily ○ 2nd episode: Physician to determine how to proceed

ANC (x10 ⁹ /L)	Dose (PO)
Platelets (x10 ⁹ /L)	Hold until PLT greater than or equal to 50: <ul style="list-style-type: none"> • 1st episode: <ul style="list-style-type: none"> ○ If within first 2 months of therapy: daSATinib 100 mg once daily, otherwise daSATinib 80 mg once daily • 2nd episode: <ul style="list-style-type: none"> ○ daSATinib 80 mg once daily • 3rd episode: <ul style="list-style-type: none"> ○ Physician to determine how to proceed • greater than or equal to 3rd month of therapy, if greater than or equal to Grade 3 thrombocytopenia: <ul style="list-style-type: none"> ○ daSATinib 80 mg once daily, once PLT greater than or equal to 50

Accelerated Phase or Blast Crisis or Ph+ ALL:

ANC (x10 ⁹ /L)		Platelets (x10 ⁹ /L)	Dose (PO)
greater than or equal to 0.5	and	greater than or equal to 10	100%
less than 0.5	and/or	less than 10	Hold until ANC greater than or equal to 1.0 & platelets greater than 20: <ul style="list-style-type: none"> • greater than 6 weeks and BM cellularity less than 10% with blasts less than 5%: <ul style="list-style-type: none"> ○ 1st episode: daSATinib 140 mg once daily ○ 2nd episode: daSATinib 100 mg once daily ○ 3rd episode: daSATinib 80 mg once daily • greater than 6 weeks and BM cellularity greater than 10% with blasts greater than 5%: <ul style="list-style-type: none"> ○ discharge daSATinib • Febrile neutropenia with signs & symptoms of sepsis: <ul style="list-style-type: none"> ○ discharge daSATinib, until recovery from sepsis

2. **Hepatic Dysfunction:**¹ Despite the lack of clinical trial data with daSATinib in patients with hepatic impairment, daSATinib should be used with caution in patients with moderate to severe hepatic dysfunction. Dasatinib is mainly metabolized through the liver, and therefore exposure to daSATinib is expected to increase in patients with hepatic impairment.

3. **Renal Dysfunction:**¹ Although the data is very limited with the use of daSATinib in patients with renal impairment, the renal clearance of daSATinib and its metabolites is estimated to be less than 4%. Therefore, no dosage adjustment for daSATinib is required in patients with renal dysfunction. The effect of dialysis on the pharmacokinetics of daSATinib has not been studied.

PRECAUTIONS:¹⁻²

1. **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively. **Bone marrow suppression**, especially neutropenia, thrombocytopenia, and anemia is more common in patients with advanced CML or Ph+ ALL, than in patients with chronic phase CML. Management includes dose reduction, interruption or (rarely) discontinuation of daSATinib.
2. **Pleural Effusion:** May occur in up to 14% of patients (10% grades 1-2, 4% grades 3-4). Grade 3-4 pleural effusion is more prevalent (10%) in patients experiencing blast crisis. Chest x-rays should be performed on patients that exhibit signs and symptoms of pleural effusion, including dyspnea or dry cough. Additionally, treatment of mild-moderate pleural effusion can be effectively managed through transient daSATinib discontinuation or with the use of diuretics. Dasatinib therapy should be withheld in patients with severe pleural effusion, until the condition improves or resolves. The severity of the pleural effusion will dictate when and at what reduced dosage daSATinib treatment should be resumed. Oxygen therapy, peritoneo-venous shunts, and thoracentesis can also be used in patients with severe pleural effusion, but are generally not utilized clinically. The median duration of daSATinib discontinuation for all grades of pleural effusion has been demonstrated to be 27 days (range of 4-113 days).
3. **Pulmonary arterial hypertension (PAH):** serious cases have been reported post-marketing. Patients who develop symptoms such as dyspnea and fatigue after initiation of daSATinib should be evaluated for more common etiologies such as pleural effusion, pulmonary edema, anemia, or lung infiltration. Dasatinib should be withheld during evaluation if symptoms are severe, and permanently discontinued if PAH is confirmed.
4. **Hemorrhaging:** May occur in about 22% of patients treated with daSATinib (15% grades 1-2, 7% grades 3-4). Grade 3-4 hemorrhaging may be more prevalent in accelerated phase (8%) and blast crisis (9%) CML patients, as well as Ph+ ALL patients (12%). Severe hemorrhaging has been reported mainly in the form of life-threatening gastrointestinal bleeding, and cerebral hemorrhage. Serious bleeding has also been associated with thrombocytopenia. Mild-moderate bleeding may include bleeding from the nose, gums, and excessive menstrual bleeding. Patients should undergo regular blood count testing, and inform their physicians of any form of bleeding/bruising. Dasatinib therapy should be withheld in patients, experiencing severe bleeding, until the condition improves or resolves. Blood transfusions should be provided, and elective invasive procedures delayed to minimize potential complications. The severity of the bleeding will dictate when and at what reduced dosage daSATinib treatment may be resumed (please also refer to the section under Exclusions).
5. **Diarrhea:** May occur in about 32% of patients (28% grades 1-2, 4% grades 3-4). Grades 3-4 diarrhea may be slightly more prevalent in daSATinib-treated accelerated phase (5%) and blast crisis (6%) patients. Sources of infection should be ruled out and standard supportive care and antidiarrheal treatment provided, when indicated for the management of diarrhea. Treatment with daSATinib should be withheld for patients with severe diarrhea, until the condition improves or

resolves. The severity of the diarrhea will dictate when and at what reduced dosage daSATinib treatment can be resumed.

6. **Other common adverse events (greater than 10%):** These include headaches (23%), nausea (19%), fatigue (18%), rash (17%), dyspnea (14%), asthenia (14%), pyrexia (13%), and vomiting (13%). These events were reported as severe, Grade 3 or 4, in 1-3% of total cases. Treatment with daSATinib should be withheld for patients with severe events, until their condition improves or resolves. The severity of the event will dictate when and at what reduced dosage daSATinib treatment can be resumed.
7. **Cardiotoxicity:** QT interval prolongation may occur in less than 1% of patients treated with daSATinib. Therefore, daSATinib should be used with caution in patients with pre-existing or those predisposed to QTc prolongation. Additional care should also be taken in patients experiencing or at risk for hypokalemia, hypomagnesemia, congenital long QT syndrome, those taking anti-arrhythmic medications, cumulative high-dose anthracycline therapy, or other medications that may induce QT prolongation (please also refer to the section under Exclusions).
8. **Pregnancy:** Women of childbearing potential must be advised to use highly effective contraception during treatment.
9. **HBV infection reactivation risk:** Risk of Hepatitis B Reactivation can occur in chronic HBV carriers after they receive BCR-ABL TKIs. All patients should be tested for both HBsAg and HBcoreAb. If either test is positive, such patients should be treated with lamivudine during chemotherapy and for six months afterwards. Such patients should also be monitored with frequent liver function tests and hepatitis B virus DNA at least every two months. If the hepatitis B virus DNA level rises during this monitoring, management should be reviewed with an appropriate specialist with experience managing hepatitis and consideration given to halting chemotherapy.
10. **Drug interactions:** Dasatinib inhibits CYP3A4 enzyme, which may result in a reduction in the clearance of CYP3A4 metabolized drugs (e.g., quinidine). Similarly, CYP3A4 inhibitors (e.g., erythromycin) may increase daSATinib's concentration. Conversely, coadministration of CYP3A4 inducers (e.g., phenytoin) may reduce daSATinib's concentration and lead to a subtherapeutic effect. Concomitant use of H₂-blockers (e.g., ranitidine), proton pump inhibitors (e.g., omeprazole), and antacids (e.g., MAALOX[®]) may also reduce daSATinib's concentration, due to the suppression of the gastric acid secretion. However, antacids may be used as an alternative to H₂-blockers and proton pump inhibitors if needed, provided they are spaced by at least 2 hours before or after daSATinib administration.

Call Dr. Donna Forrest or tumour group delegate at (604) 875-4863 with any problems or questions regarding this treatment program.

References:

1. Bristol-Myers Squibb Canada. Dasatinib (SPRYCEL[®]) product monograph. Montreal, Quebec: Bristol-Myers Squibb; 22 March 2007.
2. Lipton JH, Forrest DL, Gambacorti-Passerini C, Laneuville P, Leber B, Turner R. Recommendations for the management of imatinib-resistant/intolerant chronic myeloid leukemia (CML) patients with the kinase inhibitor, SPRYCEL (Dasatinib). Consensus Statement 2007.

Appendix. Funding Algorithm of Chronic Myeloid Leukemia (CML) and Ph+ Acute Lymphoblastic Leukemia (ALL)

