BC Cancer Protocol Summary for Treatment of Chronic Myeloid Leukemia and Ph+ Acute Lymphoblastic Leukemia Using iMAtinib

Protocol Code	*LKCMLI*
Tumour Group	*Leukemia*
Contact Physician	*Dr. Donna Forrest*

ELIGIBILITY:

- **Unequivocal diagnosis of CML:** Philadelphia (Ph) chromosome or molecular equivalent by conventional cytogenetics, FISH, or polymerase chain reaction **must** be present.
  - Chronic phase:
    - Newly-diagnosed, previously untreated CML, including patients who may be candidates for stem cell transplantation, while decisions regarding transplant are pending.
    - Patients currently receiving interferon (or any other therapy including hydroxyUREA, low dose cytarabine, etc.), who have obtained less than a complete cytogenetic remission on the drug or who have become intolerant to the drug (NCI Grade 3 intolerance to interferon for greater than 2 weeks).
    - Patients with hematologic resistance (less than complete hematologic response) or refractoriness (rising WBC while on interferon)
    - Patients who experience cytogenetic or hematologic relapse post allogeneic stem cell transplantation, for whom donor leukocyte infusions are inappropriate, impossible, or ineffective.
  - Accelerated or blast phase, as defined by usual clinical criteria, while on any therapy including hydroxyUREA, interferon, or after stem cell transplant.
- Ph+ acute leukemia, whether or not assumed to have evolved from (unrecognized) CML.
- May be used in combination with busulfan, dexamethasone, hydroxyUREA, interferon, melphalan or predniSONE

EXCLUSIONS:

- Significant comorbid illnesses, which preclude quality of life (e.g., not appropriate for elderly patients with other life-limiting diseases or significantly impaired cognitive states).
- Pregnancy

TESTS:

- Baseline: CBC & Diff, ALT, total bilirubin, urea, creatinine, body weight, bone marrow examination for cytogenetic analysis, FISH, and RT-PCR (for BCR/ABL transcripts).
- **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, HBsAb, HBcoreAb
- *Monitoring for disease progression:*
  - CBC & Diff: 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
  - creatinine, uric acid, ALT, total 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 even for patients in stable MMR (this will be reviewed again after 12 months of generic iMAtinib has been used)
  - Bone marrow aspirate and biopsy: at diagnosis, then as clinically indicated
- *Monitoring for dose modifications*: CBC & diff, ALT, total 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
- If clinically indicated: HBV viral load (see protocol SCHBV)

PREMEDICATIONS:

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

SUPPORTIVE MEDICATIONS:

- Moderate risk of hepatitis B reactivation. If HBsAg or HBcoreAb positive, follow hepatitis B prophylaxis as per SCHBV.

TREATMENT:

Drug	Disease	Dose	BC Cancer Administration Guideline
iMAtinib	CML chronic phase	400 mg daily	PO
	CML accelerated phase	600 mg daily (may increase to 400 mg twice daily in non-responders).*	
	CML blast phase		
	Ph+ acute leukemias		

*Discontinue, if no response after 90 days.

DOSE MODIFICATIONS:

1. Hematological:

Chronic Phase:

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Dose (PO)
greater than or equal to 1	and	greater than or equal to 50	100%
less than 1	or	less than 50	Hold until ANC greater than or equal to 1.5 and platelets greater than or equal to 75, then: 1st occurrence: resume at 400 mg daily. 2nd occurrence: resume at 300 mg daily.

Accelerated Phase or Blast Crisis:

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	or	less than 10	▪ If cytopenia is unrelated to disease, reduce dose to 400 mg daily. ▪ If cytopenia persists for 2 weeks, reduce dose further to 300 mg daily. ▪ If cytopenia persists for 4 weeks, hold until ANC greater than or equal to 1 and platelets greater than or equal to 20, then resume at 300 mg daily.

2. Hepatic Dysfunction

Bilirubin		ALT	Dose
less than or equal to 3 x ULN	and	less than or equal to 5 x ULN	100%
greater than 3 x ULN	or	greater than 5 x ULN	Hold until bilirubin less than 1.5 x ULN and ALT less than 2.5 x ULN then resume at ▪ chronic phase: 300 mg daily ▪ accelerated phase or blast crisis: 400 mg daily

ULN = upper limit of normal

3. **Renal Dysfunction:** No dose modification required, but iMAtinib is associated with renal toxicity (see Precautions).

PRECAUTIONS:

1. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively. **Bone marrow suppression**, especially neutropenia and thrombocytopenia, is more common at higher doses (greater than or equal to 750 mg/day), and in blast crisis or accelerated phase, compared to chronic phase when treating chronic myeloid leukemia. Management is dose reduction, interruption or (rarely) discontinuation of iMAtinib.
2. **Edema** is most frequently periorbital or in lower limbs, but may include pleural effusion, ascites, pulmonary edema, and rapid weight gain with or without superficial edema. Body weight is used to assess fluid retention, which appears to be dose related (especially greater than or equal to 600 mg /day), more common in the elderly, and may be serious or life threatening. Edema is managed with diuretics, other supportive measures or iMAtinib dose reduction.
3. **Hepatotoxicity** with severe elevations of transaminases or bilirubin may be life threatening. Risk may be increased, when iMAtinib is combined with other potentially hepatotoxic drugs. Management is dose reduction, interruption (median duration one week), or discontinuation (less than 0.5%) of iMAtinib.
4. **Renal toxicity** is more likely in accelerated phase or blast crisis (1.3%) than chronic phase (0.2%). Dose reduction may be required.
5. **Cardiac toxicity** in the form of CHF or reduced cardiac ejection fraction has been reported infrequently (less than 1%) in patients receiving iMAtinib. For patients with a previous history of cardiac disease or those with known cardiac risk factors (hypertension, diabetes, etc.), caution should be used when prescribing iMAtinib to these patients. Close clinical follow-up is recommended and any signs of CHF should be thoroughly investigated.
6. **Drug interactions** may occur, as iMAtinib is a potent competitive inhibitor of Cytochrome P450 enzymes (see BC Cancer Drug Manual).
7. **Pregnancy:** Women of childbearing potential must be advised to use highly effective contraception during treatment.

8. **Hepatitis B Reactivation:** See SCHBV protocol for more details.
9. **Progressive renal dysfunction:** loss of function may be greatest in first year and may contribute to development or worsening of some kidney diseases

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

References:

1. Druker BJ, Talpaz M, Resta DJ et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. N Engl J Med 2001;344:1031-7.
2. Druker BJ, Sawyers CL, Kantarjian H et al. Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome. N Engl J Med 2001;344:1038-42.
3. O'Brien SG, Guilhot F, Larson RA et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic myeloid leukemia. N Engl J Med 2003; 348:994-1004.