Regimen Monograph

A - Regimen Name

IMAT Regimen

Imatinib

Disease Site

Hematologic
Leukemia - Acute Lymphoblastic (ALL)

Intent

Curative
Palliative

Regimen Category

Evidence-Informed :

Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.

Rationale and Uses

- Added to acute leukemia protocols for patients with newly diagnosed, Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL).
- As monotherapy for patients with relapsed or refractory Ph+ALL.
- There is insufficient evidence to recommend use as maintenace therapy post-transplant.

Supplementary Public Funding

iMAtinib
ODB - General Benefit (iMAtinib - Refer to listed Health Canada indications for generic imatinib formulations. Patients must meet generic substitution policies for access to Gleevec.) (ODB Formulary)

back to top

B - Drug Regimen

iMAtinib	600* mg	PO	Daily

*dose may be increased to 400 mg PO BID if tolerated and appropriate (disease site group recommendation)

back to top

C - Cycle Frequency

CONTINUOUS TREATMENT

Until disease progression or unacceptable toxicity.

back to top

D - Premedication and Supportive Measures

Antiemetic Regimen: Minimal – No routine prophylaxis; PRN recommended

Febrile Neutropenia Risk: Low

Other Supportive Care:

- Patients at risk of tumour lysis syndrome should have appropriate prophylaxis and be monitored closely.
- Patients should be tested for HBV infection prior to initiating treatment. Carriers of HBV must be monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy.

Also refer to CCO Antiemetic Recommendations.

back to top

E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated. The following recommendations have been adapted from clinical trials or product monographs and may be considered.

Dosage with toxicity

Dose levels are 200mg, 300mg, 400mg, 600mg, and 800mg.

An 800 mg daily dose should be given as 400 mg BID, to reduce iron exposure.

Toxicity	Action
Fluid retention (grade 3,4)	Hold until ≤ grade 1; resume with 1 dose level ↓
Rash (grade 3, 4)	Hold until ≤ grade 1; resume with 1 dose level ↓ or discontinue
Hypotension / Hypersensitivity reaction	Hold, treat supportively, consider steroids
Bleeding	Hold; consider discontinuing if severe
Pneumonitis	Hold, investigate, consider discontinuing if confirmed
DRESS	Consider discontinuing
Increased LFTs (bilirubin > 3 x ULN or ASL/ALT > 5 x ULN)	Hold until bilirubin < 1.5 x ULN and AST/ALT < 2.5 x ULN, then restart at ↓ one dose level

Dosage with myelosuppression:

	ANC (x 10^9/L)	Platelets (x 10^9/L)	Action
Ph+ ALL	< 0.5	<10	• If related to disease (i.e., marrow), consider escalating dose • If unrelated to leukemia ↓ one dose level • If no recovery in 2 weeks, ↓ further by one dose level • If no recovery in further 2 weeks: ◦ Hold until ANC ≥ 1 x 10^9/L and platelets ≥ 20 x 10^9/L and then resume treatment without further dose reduction

Hepatic Impairment

Imatinib is excreted via the liver and increased exposure is likely in the presence of hepatic impairment.

Hepatic impairment	Suggested imatinib dose
Mild to moderate (bilirubin > 1.5-3 x ULN or AST/ALT > ULN and bilirubin ≤ 1.5 x ULN)	Start at 400 mg. May consider escalation if tolerated and appropriate.
Severe (bilirubin > 3 x ULN or AST/ALT > 5 x ULN)	Start at 200 mg. If no toxicity, may increase to 300 mg.

Renal Impairment

Imatinib is not excreted via the kidney to a significant extent; however, increased exposure and adverse effects are correlated with renal impairment. Exercise caution in patients with mild to moderate renal impairment.

CrCl (ml/min)	Suggested imatinib dose
20-59	Start at 400 mg. For CrCl 40-59, may consider escalation if tolerated and appropriate
< 20	Discontinue

Dosage in the Elderly

There is no evidence of an increase in toxicity in patients older than 65 years compared to younger patients.

back to top

F - Adverse Effects

Refer to imatinib drug monograph(s) for additional details of adverse effects

The following adverse effects were reported in patients with newly diagnosed CML. As per the imatinib product monograph, adverse reactions for Ph+ALL were similar to those reported for CML.

Very common (≥ 50%)	**Common (25-49%)**	**Less common (10-24%)**	**Uncommon (< 10%),** **but may be severe or life-threatening**
• Fluid retention (including effusions; may be severe) • Musculoskeletal pain • Nausea, vomiting	• Diarrhea • Rash (may be severe) • Fatigue • Headache • Abdominal pain • Infection (including opportunistic)	• Abnormal electrolytes • Cough, dyspnea (may be severe) • Dizziness • Flu-like symptoms • Depression/anxiety • Insomnia • Increased LFTs (may be severe) • Myelosuppression +/- bleeding (may be severe, including CNS, GI hemorrhage) • Dyspepsia • Constipation	• Arterial thromboembolism • Venous thromboembolism • Cardiotoxicity • Arrhythmia • Pericarditis • Pulmonary hypertension • GI obstruction, perforation • Hypersensitivity • Tumour lysis syndrome • DRESS • Rhabdomyolysis • Renal failure • Optic neuritis • Pancreatitis • Avascular necrosis

back to top

G - Interactions

Refer to imatinib drug monograph(s) for additional details

- Imatinib is mainly metabolized by CYP3A4. Inhibitors and inducers of CYP3A4 may affect imatinib exposure, and should be used with caution.
- Imatinib inhibits CYP3A4 and CYP2D6 and may affect the concentration of substrates of these enzymes. Caution if used with drugs with a narrow therapeutic index.
- Imatinib inhibits CYP2C9 at high doses, and may affect the concentration of CYP2C9 substrates (e.g. warfarin). Caution and monitor closely.
- Imatinib can increase the risk of bleeding when used with antiplatelet agents or anticoagulants through an additive effect. Avoid if possible, or monitor closely.
- Imatinib inhibits o-glucuronidation of acetaminophen and can increase acetaminophen exposure, increasing risk of hepatotoxicity (fatal case reported). Caution, and monitor LFTs.

back to top

H - Drug Administration and Special Precautions

Refer to iMAtinib drug monograph(s) for additional details

Administration:

- Should be administered orally with meal(s) and a large glass of water to reduce gastric irritation.
- Doses < 800mg should be given once daily; total daily doses of 800mg should be given as 400mg twice daily to reduce exposure to iron.
- If a dose is missed, the patient should not take the missed dose, but take the next prescribed dose.
- If unable to swallow, may be dispersed in water or apple juice (use 50 mL for 100 mg tablet, and 200 mL for a 400 mg tablet) immediately before drinking this mixture. Then, rinse the container with water or apple juice and drink this, to ensure no trace of the tablet is left.
- Avoid grapefruit, starfruit, Seville oranges, their juices or products during treatment.

Contraindications:

• Patients with hypersensitivity to imatinib or to any other components of this product

Warnings/precautions:

- Consultation with a liver disease expert is recommended prior to starting imatinib in chronic HBV carriers (including those with active disease), and for patients who test positive for HBV infection while on treatment
- Imatinib results in serious fluid retention in 6% of patients, especially with higher doses. Patients should be weighed and monitored regularly. Patients with pre-existing cardiac disease, risk factors for cardiac failure or the elderly should be monitored carefully and be treated appropriately.
- Bleeding, including GI, CNS and intra-tumoural, have been reported; concomitant use of warfarin or antiplatelet agents should be avoided. Consider the use of LMWH rather than warfarin if anticoagulation is mandatory.
- Exercise caution if drugs that may increase bleeding (e.g. anticoagulants, antiplatelets or prostacyclins) must be used.

Pregnancy and Lactation:

- Imatinib is contraindicated during pregnancy. Spontaneous abortions have been reported in women who have taken imatinib. Highly effective contraception (failure rate < 1%) is recommended for both sexes during treatment, and for at least 6 months (general recommendation) after imatinib cessation.
- Women of childbearing potential should have a negative serum or urine pregnancy test (with a sensitivity of at least 25 mIU/ml) within one week before starting therapy.
- Breastfeeding is not recommended. Imatinib and/or its metabolites are excreted in human milk.
- Fertility may be affected in males.

back to top

I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

- Brain imaging for patients suspected of having subdural hemorrhage; as clinically indicated
- CBC; weekly for first month, biweekly for second month, and as indicated thereafter (e.g. every 2 to 3 months)
- Electrolytes, serum creatinine and creatinine clearance; baseline and monthly or as clinically indicated
- INR for patients taking warfarin, especially when starting treatment and with imatinib dose adjustments; baseline and regular

- Liver function tests; baseline and monthly or as clinically indicated
- LVEF, in patients with known underlying heart disease or in elderly patients; baseline and as clinically indicated
- Platelet counts and prothrombin time when imatinib is used concurrently with anticoagulants, prostacyclins, or other medications that increase bleeding risk; baseline and periodic
- TSH levels in patients with previous thyroidectomy or patients on replacement therapy; baseline and regular
- Serum or urine pregnancy test in women of childbearing potential; within one week before starting treatment
- HBV infection status: Prior to starting treatment; consult infectious disease if positive
- For carriers of HBV: signs and symptoms of active HBV infection; At each visit during treatment and for several months after treatment discontinues
- Clinical assessment of fluid retention (including weight monitoring), bleeding, infection, cardiac effects, thromboembolism, rhabdomyolysis, tumour lysis syndrome and gastrointestinal effects, pneumonitis, rash; at each visit

- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

- EKG and troponin in patients with hypereosinophilia and cardiac involvement

back to top

J - Administrative Information

Outpatient prescription for home administration

back to top

K - References

Couban S, Savoie L, Mourad YA, et al. Evidence-based guidelines for the use of tyrosine kinase inhibitors in adults with Philadelphia chromosome-positive or BCR-ABL-positive acute lymphoblastic leukemia: a Canadian consensus. Curr Oncol. 2014 Apr;21(2):e265-309.

Imatinib drug monograph, Cancer Care Ontario.

Lee S, Kim YJ, Min CK, et al. The effect of first-line imatinib interim therapy on the outcome of allogeneic stem cell transplantation in adults with newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia. Blood. 2005 May 1;105(9):3449-57.

Ottmann OG, Druker BJ, Sawyers CL, et al. A phase 2 study of imatinib in patients with relapsed or refractory Philadelphia chromosome-positive acute lymphoid leukemias. Blood. 2002 Sep 15;100(6):1965-71.

Yanada M, Takeuchi J, Sugiura I, et al; Japan Adult Leukemia Study Group. High complete remission rate and promising outcome by combination of imatinib and chemotherapy for newly diagnosed BCR-ABL-positive acute lymphoblastic leukemia: a phase II study by the Japan Adult Leukemia Study Group. J Clin Oncol. 2006 Jan 20;24(3):460-6.

April 2024 Changed imatinib to ODB General Benefit

back to top

M - Disclaimer

Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.

Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

Regimen Monographs

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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back to top