Imatinib (CML)

Indication

First line treatment of Philadelphia chromosome positive (Ph+) chronic myeloid leukaemia (CML) in patients where bone marrow transplantation is not considered as the first line of treatment.

Ph+ CML in chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis.

(NICE TA251)

Newly diagnosed Ph+ acute lymphoblastic leukaemia (Ph+ ALL) integrated with chemotherapy.

Relapsed or refractory Ph+ ALL as monotherapy.

Myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements.

Advanced hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL) with FIP1L1-PDGFRα rearrangement.

(Funding via CDF)

ICD-10 codes

Codes with a pre fix C92.1, C91.0, D72.1, D47.1

Regimen details

Indication	Drug	Dose	Route
CML	Imatinib	400mg OD	PO
CML advanced phase (acclerated/blast phase)	Imatinib	600mg OD or 400mg BD (maximum dose in absence of adverse effects)	PO
Ph+ ALL	Imatinib	600mg OD	PO
MDS/MPD	Imatinib	400mg OD	PO
HES/CEL	Imatinib	100mg OD (dose may be increased up to 400mg OD in absence of adverse effects)	PO

Cycle frequency

Continuous

Number of cycles

Continued until disease progression or unacceptable toxicity

Administration

Imatinib is available as 400mg and 100mg film-coated tablets.

Imatinib can cause gastrointestinal irritation therefore doses should be taken with a large glass of water, once daily, with or after food.

For patients unable to swallow imatinib tablets, the tablets may be dispersed in a glass of water or apple juice (about 200ml for a 400mg tablet) and stirred with a spoon. The suspension should be administered immediately after complete disintegration of the tablet(s).

Grapefruit and grapefruit juice should be **avoided** whilst taking imatinib.

Pre-medication

Adequate hydration and allopurinol 300mg PO OD (or 100mg OD if creatinine clearance <20mL/min) to prevent tumour lysis syndrome is recommended prior to initiation of imatinib and continued for 4 weeks.

Emetogenicity

This regimen has low emetic potential (no routine antiemetics required)

Additional supportive medication

Antiemetics if required.
Loperamide if required.

Extravasation

N/A

Investigations – pre first cycle

Investigation	**Validity period**
FBC	14 days
Coagulation screen	14 days
U + E (including creatinine)	14 days
LFTs	14 days

Confirmation of the presence of t(9;22) and/or BCR-ABL transcript (or other TKI sensitive target).

Consider initial hydroxycarbamide / leucopheresis in the event of hyperleucocytosis.

Hepatitis B (HBV) serology testing – cases of reactivation of HBV have occurred in patients who are chronic carriers of HBV after they received BCR-ABL tyrosine kinase inhibitors

Baseline evaluation of Left Ventricular Ejection Fraction (LVEF) is recommended in patients with underlying heart disease and in elderly patients.

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local policy)
FBC	3 monthly
U+E (including creatinine)	3 monthly
LFTs	3 monthly

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	**Limit**
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 50 x 10^9/L
Creatinine clearance (CrCl)	≥ 20mL/min
Bilirubin	≤ 3 x ULN
AST/ALT	≤ 5 x ULN

Dose modifications

- **Haematological toxicity**

Neutrophils	Platelets	Imatinib dose
< 1.0 x 10^9/L	< 50 x 10^9/L	Stop imatinib until neutrophils ≥ 1.5 x 10^9/L and platelets ≥75 x 10^9/L. Resume at previous dose. In the event of recurrence of neutrophils < 1.0 x 10^9/L and platelets < 50 x 10^9/L withhold imatinib until recovery as above and resume with reduced dose.

- **Renal impairment**

The renal clearance of imatinib is negligible so no dose reductions are required in mild-to-moderate renal impairment.
Although very limited information is available, patients with severe renal dysfunction (creatinine clearance < 20 mL/min) or on dialysis should start at the minimum dose. Caution is recommended in these patients.

- **Hepatic impairment**

Imatinib is primarily metabolised through the liver. Patients with mild, moderate or severe liver dysfunction should be commenced on the minimum recommended dose which can be reduced if not tolerated.

Bilirubin		ALT/AST	Imatinib dose
>3 x ULN	or	> 5 x ULN	Withhold imatinib until bilirubin < 1.5 x ULN and ALT/AST < 2.5 x ULN Resume with reduced dose.

- **Other toxicities**

Non-haematological adverse reactions
If a severe non-haematological adverse reaction develops with imatinib, treatment should be withheld until the event has resolved. Thereafter, treatment can be resumed as appropriate depending on the initial severity of the event.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression; neutropenia, thrombocytopenia, anaemia
Cardiotoxicity
Stomatitis, mucositis
Pleural effusion*
Infections (bacterial, viral and fungal)
Pulmonary fibrosis
Haemorrhage**

- **Commonly occurring side effects**

Diarrhoea
Nausea and vomiting
Headache
Periorbital oedema*
Oedema*
PPE, dermatitis, rash, eczema
Fatigue
Muscle cramps, musculoskeletal pain

*Occurrences of severe fluid retention (pleural effusion, oedema, pulmonary oedema, ascites, superficial oedema) have been reported in patients taking imatinib. Therefore, it is highly recommended that patients be weighed regularly. An unexpected rapid weight gain should be carefully investigated and if necessary appropriate supportive care and therapeutic measures should be undertaken. In clinical trials, there was an increased incidence of these events in elderly patients and those with a prior history of cardiac disease. Therefore, caution should be exercised in patients with cardiac dysfunction.

**Intra-tumoral haemorrhage or tumour-related intra-abdominal bleeding has been reported in an estimated 5% of cases and may be life-threatening. This may not be manifested as obvious gastro-intestinal bleeding as blood may be confined to the tumour, within the hepatic capsule, peritoneum or otherwise sequestered. Signs and symptoms of such an event may include hypotension, signs of hypovolaemia, fall in haematocrit, localised pain, apparent rapid increase in size of mass, and CT suggestive of bleeding. CT results should be evaluated carefully in light of this so that this syndrome is not mistaken for progressive disease.

- **Other side effects**

Anorexia
Insomnia

Significant drug interactions – for full details consult product literature/ reference texts

CYP3A4 inhibitors (e.g. ketoconazole, voriconazole, clarithromycin, erythromycin ritonavir): avoid co-administration these may increase plasma concentrations of imatinib, increasing the risk of toxicity.

Grapefruit and grapefruit juice: avoid as an inhibitor of CYP3A4 and may increase plasma concentrations of imatinib.

Inducers of CYP3A4 (e.g. rifampicin, phenytoin, carbamazepine, St Johns Wort): avoid co-administration as these may reduce exposure to imatinib.

Coumarin anticoagulants, e.g. Warfarin: Avoid if possible as may cause elevation and fluctuation in INR. Consider switching to low molecular weight heparin.

CYP3A4 substrates (e.g. statins, triazolo-benzodiazepines, dihydropyridine calcium channel blockers). Special caution is required when co-administering imatinib with substrates with a narrow therapeutic window (e.g. cyclosporin or pimozide).

Paracetamol: Imatinib inhibits paracetamol O-glucuronidation *in vitro*. Caution should be exercised when using imatinib and paracetamol concomitantly.

Levothyroxine: Imatinib may reduce exposure to levothyroxine. TSH levels should be closely monitored in patients requiring both drugs.

Simvastatin: Imatinib increases plasma levels of simvastatin – consider withholding simvastatin during treatment.

Additional comments

Women of childbearing potential must be advised to use effective contraception during treatment.

In Ph+ ALL patients, there is clinical experience of co-administering imatinib with chemotherapy, but drug-drug interactions between imatinib and chemotherapy regimens are not well characterised. Imatinib adverse eventsmay increase and it has been reported that concomitant use with L-asparaginase could be associated with increased hepatotoxicity.

References

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- Fielding AK, et al. UKALLXII/ECOG2993: addition of imatinib to a standard treatment regimen enhances long-term outcomes in Philadelphia positive acute lymphoblastic leukemia. Blood. 2014;123(6):843-850.

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