Systemic Anti-Cancer Therapy Protocol

Imatinib
Chronic Myeloid Leukaemia

PROTOCOL REF: MPHAIMAHA
(Version No: 1.0)

Approved for use in:

Newly diagnosed Philadelphia Chromosome (BCR-ABL) positive (Ph+) chronic myeloid leukaemia (CML) for who bone marrow transplantation is not considered as the first line of treatment **(NICE TA426)**.

Ph+ CML in chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis **(NICE TA70)**.

Treatment of Ph+ CML in chronic phase after failure of another tyrosine kinase inhibitor **(Unlicensed indication)**.

NICE **does not** recommend high dose imatinib for imatinib-resistant Ph+ CML. Patients currently receiving high-dose imatinib for the treatment of CML should have the option to continue that treatment until they and their clinicians consider if appropriate to stop **(NICE TA425)**.

Note that Blueteq registration is not required for any indication

Dosage:

Chronic Phase

Drug	Dose	Route	Frequency
Imatinib	400mg	PO	Daily continuous. Also see de-escalation advice below

Accelerated Phase or Blast Crisis

Drug	Dose	Route	Frequency
Imatinib	600mg	PO	Daily continuous.

De-escalation:

Certain patients with excellent responses to imatinib after several months of treatment may be eligible for de-escalation of their treatment, with the aim of stopping their treatment completely. This de-escalation procedure is managed by the CML team who follow the *DESTINY* trial (see references) Please contact the CML team for further information if required.

Administration:

- Imatinib should be taken with food with a large glass of water to reduce the risk of gastrointestinal irritation
- Tablets can be dissolved in water or apple juice (200mL), stirred and drunk as soon as possible
- Imatinib should be discontinued 1 week before major surgery and restarted when risk of bleeding is considered to be minimal.

Anti-emetic risk

Low Risk

Supportive treatments

Consider allopurinol 300mg (dose reduce for renal impairment) once daily during first cycle.

Dosing in renal and hepatic impairment

Renal	Hepatic
Renal impairment (CrCl < 60ml/min) or on haemodialysis (HD) should be given minimum starting dose of 400mg/day. Treat HD patients with caution and reduce dose if not tolerated.	Patients with hepatic impairment (bilirubin > 1.5 x ULN or AST/ALT > ULN) should be given the minimum recommended dose of 400 mg/day. The dose can be reduced if not tolerated

Interactions:

- Imatinib is a substrate of CYP3A4. Inhibitors of CYP3A4 would be expected to increase plasma levels of imatinib so caution is advised if a combination is necessary. CYP3A4 inducers including dexamethasone, phenytoin, rifampicin, St John's Wort may significantly reduce exposure to imatinib. Strong CYP3A4 inducers should be avoided.
- Imatinib inhibits CYP2D6, CYP2C9 and CYP3A4. Patients receiving medication with narrow therapeutic indexes which are substrates of CYP3A4 (e.g. ciclosporin, tacrolimus, sirolimus, fentanyl, alfentanil, bortezomib and docetaxel) or CYP2D6 (e.g. metoprolol) should be monitored and doses adjusted as appropriate.

Main toxicities:

Common: Headache, GI disturbances (nausea, vomiting, diarrhoea, dyspepsia, abdominal pain), muscle cramps, severe fluid retention (pleural effusion, oedema, pulmonary oedema, ascites, superficial oedema), rash, blurred vision, fatigue.

Less Common: Liver enzyme abnormalities

Please refer to the relevant SPC for more information on toxicities.

Investigations and treatment plan:

	Pre	Cycle 1 D1	Cycle 1 D8	Cycle 1 D15	Cycle 1 D22	Cycle 2 +	Ongoing
Informed Consent	X						
Clinical Assessment	X	X				X	Prior to every cycle
ECG and ECHO	X						If clinically indicated. Note imatinib can prolong the QTc
SOKAL score	X						
BCR-ABL PCR	X	X				X	PCR test can take a few days to process so results will be reviewed retrospectively. Monthly for the first three months, three monthly thereafter.
FBC	X	X	X	X	X	X	Prior to each cycle. A cycle may extend to six months in length once patients are stable on treatment. FBC should be taken within 7 days of prescribing but may be taken up to 14 days prior to prescription at clinician's discretion. **Prescribers must check the results prior to prescribing and document that this check has taken place in the medical notes.**
U&E & LFTs	X	X	X	X	X	X	Prior to each cycle. A cycle may extend to six months in length once patients are stable on treatment. U&E and LFTs should be taken within 7 days of prescribing but may be taken up to 14 days prior to prescription at clinician's discretion. **Prescribers must check the results prior to prescribing and document that this check has taken place in the medical notes.**
Height	X						
Weight	X	X				X	Prior to every cycle
Pregnancy test	X						If clinically indicated
Hepatitis B (including surface antigen and HB core antibody) and Hepatitis C testing	X						

Dose Modifications and Toxicity Management

Haematological toxicity:

Treat if ANC>1.0 $x10^9$ AND Plt >50 $x10^9$

Chronic phase (starting dose 400mg)	ANC <1.0 $x10^9$ and/or Platelets <50 $x10^9$	1. Resume at previous dose when 1.5 $x10^9$ cells/l and PLT ≥ 75 $x10^9$ cells/l. 2. In event of recurrence of myelosuppression, repeat delay and resume at 300mg daily.
Accelerated phase (starting dose 600mg)	ANC <0.5 $x10^9$ and/or Platelets <10 $x10^9$	1. Check if cytopenia is related to leukaemia (marrow aspirate or biopsy). 2. If unrelated to disease reduce dose to 400mg daily 3. If cytopenia continues for 2 weeks, reduce to 300mg daily. 4. If cytopenia continues for further 2 weeks interrupt treatment until ANC ≥ 1.0 x 10^9 cells/l and PLT ≥ 20 x 10^9 cells/l and resume treatment at 300mg daily.

Hepatotoxicity:

Bilirubin (Bil) > 3 x upper limit of normal (ULN) or Liver transaminases (AST/ALT) > 5 x ULN	Withold imatinib until Bil levels have returned to < 1.5 x ULN and AST/ALT< 2.5 x ULN. Resume treatment and reduce dose as follows: 400mg to 300mg Or 600mg to 400mg

References:

1. NICE (2016) TA426. https://www.nice.org.uk/guidance/ta426 Accessed 28/01/2020.
2. NICE (2016) TA425. https://www.nice.org.uk/guidance/ta425 Accessed 28/01/2020.
3. NICE (2016) TA70. https://www.nice.org.uk/guidance/ta70 Accessed 28/01/2020.

4. Novartis. Glivec 400mg film-coated tablets (Imatinib). Summary of Product Characteristics. Updated 20/05/2019. Accessed on 28/01/2020
5. MHRA (2016) Drug Safety Update: BCR-ABL tyrosine kinase inhibitors: risk of hepatitis B reactivation
6. Lancet Oncology (2019). Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Accessed on 28/01/2020
7. Lancet Haematology (2019). De-escalation of tyrosine kinase inhibitor therapy before complete treatment discontinuation in patients with chronic myeloid leukaemia (DESTINY): a non-randomised, phase 2 trial. Accessed on 28/1/2020