SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Imatinib
Chronic Myeloid Leukaemia, Hypereosinophilic Syndrome and Chronic Eosinophilic Leukaemia

PROTOCOL REF: MPHAIMAHA
(Version No.2.0)

Approved for use in:

- Newly diagnosed Philadelphia chromosome (BCR-ABL) positive (Ph+) chronic myeloid leukaemia (CML) **(NICE TA426)**
- Treatment of Ph+ CML in chronic phase after failure of another tyrosine kinase inhibitor
- Re-initiation after failed de-escalation/discontinuation of imatinib in CML
- Patients with advanced hyper-eosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL) with FIP1L1-PDGFRα rearrangement.
- NICE **does not** recommend high dose imatinib, i.e. 600mg or 800mg, 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)**.

Blueteq registration is **NOT** required for any indication

Dosage:

HES and/or CEL

Drug	Dose	Route	Frequency
Imatinib	100mg	PO	Daily continuous. Dose increase from 100 mg to 400 mg may be considered in the absence of adverse drug reactions if assessments demonstrate an insufficient response to therapy. De-escalation can be considered at consultant discretion

Chronic Phase CML

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. Dose escalation to 800mg can be considered, if required, and imatinib has been previously well tolerated

De-escalation:

Certain patients with excellent responses to imatinib after several years 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). The British Society of Haematology also provides guidance on de-escalation. 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 (50mL per 100mg), stirred and drunk as soon as possible

Emetogenic 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) CML: should be given the minimum starting dose of 400mg/day HES/CEL: initiate as normal Treat HD patients with caution and reduce dose if not tolerated.	Patients with hepatic impairment (bilirubin > 1.5 x ULN or AST/ALT > ULN) CML: should be given the minimum recommended dose of 400 mg/day. Dose can be reduced if not tolerated HES/CEL: initiate as normal

Interactions:

- Imatinib is a substrate of CYP3A4. Inhibitors of CYP3A4 (protease inhibitors, ketoconazole, itraconazole, posaconazole, voriconazole, erythromycin and clarithromycin) may 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 (ciclosporin, tacrolimus, sirolimus, fentanyl, alfentanil, bortezomib and docetaxel) or CYP2D6 (e.g. metoprolol) should be monitored and doses adjusted as appropriate.

Please refer to the SPC for more information on interactions.

Main toxicities:

Imatinib
Myelosuppression, 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, dizziness, taste disturbance, fatigue, sleep disturbance. 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 three 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 three 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:

Give on day 1 if:

ANC >1.0 x10^9/L	Platelets >50 x10^9/L

HES/CEL (starting dose 100mg)	ANC <1.0 x10^9/L and/or Platelets <50 x10^9/L	1. Stop imatinib until ANC ≥ 1.5 x 10^9/L and platelets ≥ 75 x 10^9/L. 2. Resume imatinib at previous dose
Chronic phase (starting dose 400mg) HES/CEL (at dose 400mg)	ANC <1.0 x10^9/L and/or Platelets <50 x10^9/L	1. Stop imatinib until ANC ≥ 1.5 x 10^9/L and platelets ≥ 75 x 10^9/L. 2. Resume imatinib at previous dose 3. In event of recurrence of myelosuppression (ANC <1.0 x10^9/L and/or platelets <50 x10^9/L), repeat delay and resume imatinib at 300mg daily once ANC ≥ 1.5 x 10^9/L and platelets ≥ 75 x 10^9/L.
Accelerated phase (starting dose 600mg)	ANC <0.5 x10^9/L and/or Platelets <10 x10^9/L	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 a further 2 weeks interrupt treatment until ANC ≥ 1.0 x 10^9/L and PLT ≥ 20 x 10^9/L and resume imatinib 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 01/06/2023.
2. NICE (2016) TA425. https://www.nice.org.uk/guidance/ta425 Accessed 01/06/2023.
3. NICE (2016) TA70. https://www.nice.org.uk/guidance/ta70 Accessed 01/06/2023.
4. Amarox. Imatinib 400 mg film-coated tablets. Summary of Product Characteristics. Updated 07/06/22. Accessed on 01/06/2023
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.
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
8. British Journal of Haematology (2020). A British Society for Haematology Guideline on the diagnosis and management of chronic myeloid leukaemia

Circulation/Dissemination

Date added into Q-Pulse	For completion by DCM
Date document posted on the Intranet	For completion by DCM

Version History

		Author name and designation	Summary of main changes
11th May 2020	1.0	**Mark Nelson**	**Protocol created**
Aug 2023	2.0	**Jade Marsh**	**Moved into new protocol template. Indications updated. HES/CEL information added.**