Chemotherapy Protocol

Chronic Myeloid Leukaemia

Nilotinib (chronic phase)

Regimen

- CML – Nilotinib (chronic phase)

Indication

- As an option for the treatment of patients with newly diagnosed Philadelphia-chromosome-positive chronic myelogenous leukaemia (CML) in the chronic phase.

- As an option for the treatment of Philadelphia-chromosome-positive CML in the chronic or accelerated phase in patients who have become resistant to or intolerant of other tyrosine kinase inhibitors.

Toxicity

Drug	Adverse Effect
Nilotinib	Headache, nausea, upper abdominal pain, rash, pruritis, alopecia, myalgia, fatigue, hypophosphataemia, hyperbilirubinaemia.

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Monitoring

Drugs

- FBC, U&Es and LFTs at baseline prior to starting nilotinib therapy then every two weeks for the first two months, then monthly for two months, then increasing to three monthly in patients with a stable response, or as clinically indicated.

- Magnesium, potassium and phosphate levels at baseline, then periodically throughout therapy. If abnormal at baseline these should be corrected before starting nilotinib therapy.

- Caution should be taken in patients with known cardiovascular pathology and all patients should have a cardiovascular risk assessment performed at diagnosis. An alternative tyrosine kinase inhibitor should be considered in those deemed to have a high risk of cardiovascular disease

- A baseline ECG prior to starting nilotinib is advised for all patients. Those patients with a prolonged QTc interval, and those at high risk for developing a prolonged QTc interval should be treated with extreme caution and may require regular ECG surveillance during nilotinib therapy.

- Blood pressure at each clinic visit.

- Hepatits B, C and HIV status should be checked prior to starting nilotinib therapy. Patients who are carriers of HBV and those with active disease should be discussed with a consultant hepatologist prior to starting nilotinib therapy.

- Serum lipase or amylase monthly initially, then three monthly, or as clinically indicated.

- Blood lipid profile at baseline and then at month three and month six. For patients on chronic treatment continue yearly blood lipid monitoring.

- TSH at baseline, then yearly or as clinically indicated.

Dose Modifications

The dose modifications listed are for haematological, liver and renal function and drug specific toxicities only. Dose adjustments may be necessary for other toxicities as well.

Please discuss all dose reductions / delays with the relevant consultant before prescribing, if appropriate. The approach may be different depending on the clinical circumstances.

Haematological

Dose modifications for haematological toxicity in the table below are for general guidance only. Always refer to the responsible consultant as any dose reductions or delays will be dependent on clinical circumstances and treatment intent.

Haematological toxicity usually presents within eight weeks of starting nilotinib therapy and occurs more frequently in patients with imatinib resistance/intolerance.

Consider blood transfusion if the patient is symptomatic of anaemia or where the haemoglobin is less than 8g/dL (80g/L).

Chronic Phase

Neutrophils ($x10^9$/L)	**Dose Modifications**
Less than 1	1. Stop nilotinib and monitor blood counts. 2. If neutrophils recover to greater than or equal to $1x10^9$/L within two weeks, resume on 300mg twice a day. 3. If neutrophils remain less than $1x10^9$/L resume at a reduced dose of 400mg once a day.
Platelets ($x10^9$/L)	**Dose Modifications**
Less than 50	1. Stop nilotinib and monitor blood counts. 2. If platelets recover to greater than or equal to $50x10^9$/L within two weeks, resume on 300mg twice a day. 3. If platelets remain less than $50x10^9$/L resume at a reduced dose of 400mg once a day.

Hepatic Impairment

Drug	Bilirubin µmol/L		AST/ALT units	Dose (% of original dose)
Nilotinib	Greater than 3xULN	And / or	Greater than 5xULN	Reduce dose to 400mg once a day, or interrupt therapy

For grade 3-4 serum lipase or amylase elevations, reduce the nilotinib dose to 400mg once a day, or interrupt treatment.

Renal Impairment

No dose adjustments are necessary.

Regimen

28 day cycle until disease progression or intolerance (12 cycles will be set in Aria)

Chronic Phase

Drug	Dose	Days	Administration
Nilotinib	300mg twice a day	Days 1-28 (inclusive)	Oral

The dose of nilotinib in those in chronic phase who are intolerant of or resistant to prior therapies is 400mg twice a day.

Dose Information

- Nilotinib is available as 150mg and 200mg hard capsules.

Administration Information

- Nilotinib should be taken twice a day approximately 12 hours apart and must not be taken with food. The hard capsules should be swallowed whole with water. No food should be consumed for 2 hours before the dose is taken and no food should be consumed for at least one hour after the dose is taken.

- For patients who are unable to swallow hard capsules, the content of each hard capsule may be dispersed in one teaspoon of apple sauce (puréed apple) and should be taken immediately. Not more than one teaspoon of apple sauce and no food other than apple sauce must be used.

Additional Information

- The National Patient Safety Alert on oral chemotherapy (NPSA/2008/RRR001) must be followed in relation to nilotinib.

- It must be made clear to all staff, including those in the community, that nilotinib should only be prescribed under the supervision of a consultant haematologist.

- Elimination of nilotinib is mainly through hepatic metabolism. Nilotinib is a substrate and an inhibitor of CYP3A4. Therefore, concomitant use of medicines that

induce CYP3A4 or potently inhibit CYP3A4 is not recommended by the manufacturer.

- Nilotinib interacts with many other agents. Always check for drug interactions.

Coding

- Procurement – X71.3
- Delivery – X73.1

References

1. Novartis Pharmaceuticals Limited (2016). Tasigna 150mg Hard Capsules Summary of Product Characteristics. Electronic Medicines Compendium. Online at http://www.medicines.org.uk/emc/medicine/24089, accessed 12 September 2016.
2. Novartis Pharmaceuticals Limited (2016). Tasigna 200mg Hard Capsules Summary of Product Characteristics. Electronic Medicines Compendium. Online at http://www.medicines.org.uk/emc/medicine/20827, accessed 21 September 2016.
3. National Institute for Health and Care Excellence (2012) Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia (CML) (part review of NICE technology appraisal guidance 70), and dasatinib and nilotinib for people with CML for whom treatment with imatinib has failed because of intolerance. [TA241]. London: National Institute for Health and Care Excellence.
4. National Institute for Health and Care Excellence (2012) Dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of chronic myeloid leukaemia. [TA251]. London: National Institute for Health and Care Excellence.

REGIMEN SUMMARY

Two protocols will be set up in ARIA, one for chronic and one for the accelerated phase

Nilotinib (chronic phase)

Nilotinib (chronic)

Cycle 1 onwards

Day 1-28

1.Nilotinib 300mg twice a day oral
Administration Information
Oral chemotherapy

The hard capsules should be swallowed whole with water. No food should be consumed for 2 hours before the dose is taken and no food should be consumed for at least one hour after the dose is taken.

Please supply the nearest original whole pack according to local practice

The dose of nilotinib in those in chronic phase who are intolerant of or resistant to prior therapies is 400mg twice a day.

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	January 2017	None	Eleanor Taylor Pharmacist	Dr Andrew Duncombe Consultant Haematologist

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

Hampshire Hospitals NHS Foundation Trust
NHS Isle of Wight
Portsmouth Hospitals NHS Trust
Salisbury NHS Foundation Trust
University Hospital Southampton NHS Foundation Trust
Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors that occur as a result of following these guidelines.