Hull and East Yorkshire and North Lincolnshire NHS Trusts Haematology Multidisciplinary Team Guideline and Pathway

Chronic Myeloid Leukaemia

1 BACKGROUND

The Hull and North Lincolnshire Haematology Multidisciplinary team manages patients with haematological malignancies on three sites, Diana Princess of Wales Hospital Grimsby, the Queens Centre for Haematology and Oncology at Castle Hill Hospital Hull and East Yorkshire Hospitals NHS Trust and Scunthorpe Hospital.

Levels of service provided in these organisations is as defined in the NICE guidance "Haematological Cancers: improving outcomes NG47" 25th May 2016.

Low-intermediate intensity chemotherapy is delivered in Grimsby, the Queens Centre Castle Hill Hospital and Scunthorpe Hospital.

High-intensity chemotherapy and autologous stem cell transplantation is delivered at the Queens Centre, Castle Hill Hospital.

Allogeneic stem cell transplantation is delivered in the regional transplant centres in Leeds, Nottingham and Sheffield.

Tyrosine kinase inhibitor therapy, Interferon, Busulphan and Hyrdroxycarbimide are delivered in sites offering low-to intermediate intensity chemotherapy.

High intensity chemotherapy including, but not limited to, DA, FLAG, FLAG-Ida, intermediate and high dose Cytarabine will only be delivered in the high intensity chemotherapy unit in Queens Centre, Castle Hill Hospital.

2 POLICY / PROCEDURE / GUIDELINE DETAIL

The Hull and North Lincolnshire MDT has decided that patients with chronic myeloid leukaemia (CML) will be monitored in line with the European Leukaemia Net CML recommendations;

https://www.leukemia-net.org/content/leukemias/cml/recommendations/index_eng.html

However the treatment will follow NICE pathways and guidance;

https://pathways.nice.org.uk/pathways/blood-and-bone-marrow-cancers/leukaemia

Guidance on the use of Imatinib for chronic myeloid leukaemia

Technology appraisal guidance [TA70] Published date: 22 October 2003 last updated: 21 January 2016.

https://www.nice.org.uk/guidance/ta70

Dasatinib, Nilotinib and high-dose Imatinib for treating Imatinib-resistant or intolerant chronic myeloid leukaemia

Technology appraisal guidance [TA425] Published date: 21 December 2016

https://www.nice.org.uk/guidance/ta425

Dasatinib, Nilotinib and Imatinib for untreated chronic myeloid leukaemia

Technology appraisal guidance [TA426] Published date: 21 December 2016

https://www.nice.org.uk/guidance/ta426

Bosutinib for previously treated chronic myeloid leukaemia

Technology appraisal guidance [TA401] Published date: 24 August 2016

https://www.nice.org.uk/guidance/ta401

Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia

Technology appraisal guidance [TA451] Published date: 28 June 2017

https://www.nice.org.uk/guidance/ta451

OUTLINE MANAGEMENT FOR PHILADELPHIA POSITIVE (PH+VE) CHRONIC MYELOID LEUKAEMIA

Definitions of disease and primary therapy

Patients in chronic phase (CP)

- All new patients should be, if possible, offered entry into a study of first line therapy.
- Test all patients starting on tyrosine kinase inhibitors (TKI) for Hepatitis B
- Assess cardiovascular risk in all patients using QRISK2 and refer to primary care if QRISK2 score >20 and check annually thereafter.
- Take baseline samples for blood glucose and lipase for patients started on Nilotinib.
- All patients should be well hydrated and receive Allopurinol 300mg daily.
- In non-trial patients, initial cytoreductive therapy should be with Imatinib 400 mg daily for those patients with a low or intermediate Sokal risk score.
- Consider second generation tyrosine kinase inhibitors (2^{nd} Gen-TKIs) in patients with a high Sokal score, but the potential benefit needs to be considered versus cardiovascular risk status. Currently only Nilotinib (at a dose of 300mg bd) is NICE approved for this indication.
- Initial therapy with Hydroxycarbamide 0.5g – 2g daily can be considered for patients awaiting confirmation of diagnosis or as an interim measure if contemplating entry into a clinical trial.
- Male and female patients should be counselled regarding fertility. There is very little evidence to support sperm storage before starting TKI. Female patients should not become pregnant on TKI but information regarding how pregnancy can be managed when stable on treatment.

Monitoring of therapy

- FBC, U&Es, LFTs and uric acid weekly for the 1st 4 weeks, then reduced frequency depending on response.
- Peripheral blood RT PCR should be carried out every 3 months. 10ml of EDTA blood is required.
- Bone marrow (BM) examination with cytogenetics should be carried out when the patient has been on TKI for 6 months. If BCR-ABL is not <1% with Ph+ (CCyR) then a further BM should be taken at 12 months.

- Patients not achieving an optimal response should be considered for a change in therapy, which is mandatory for patients deemed to be failing therapy. Options depend on the first line therapy. Nilotinib should be prescribed for those failing Imatinib therapy. For those failing Nilotinib, Ponatinib should be given if a T315I mutation is detected, for others consideration should be given to either Dasatinib or Bosutinib - this may require an IFR application.

Patients in Accelerated Phase (AP)

- Patients presenting in the accelerated phase of CML should receive Nilotinib 400mg bd, after any cardiovascular risk issues have been considered, as outlined above. In patients deemed to have an unacceptably high risk of cardiovascular events, Imatinib 600mg daily should be given which is associated with a reported progression-free survival rate of 67% at 12 months, and overall survival of 66% at 36 months.

Patients in Blast Crisis (BC)

- Patients presenting in blast crisis present a difficult management problem. The best responses have been reported to Imatinib 600-800mg daily, with reported 12-month survival rates of 32%. Major cytogenetic responses have been reported in 16% of patients, and complete cytogenetic responses in 7%. Dasatinib is also licensed for this indication, at a dose of 70mg bd, but IFR approval may be required. Nilotinib is not licensed in blast crisis.

- NICE do not recommend continued use of Imatinib in patients presenting in CP who progress to AP or BC after exposure to the drug. Management of such cases should be discussed with the MDT lead for leukaemia, but a second-generation tyrosine kinase inhibitor (2G – TKI), (Dasatinib or Bosutinib - IFR approval may be required) should be given while assessing BMT options. Consideration should be given to acute leukaemia type therapy (as for AML or ALL depending on phenotype) and rarely, autologous stem cell transplantation.

Cardiovascular side effects with second generation TKI

- Data from clinical trials has shown an association between second generation TKIs and cardiovascular adverse events. These included ischaemic heart disease, cerebrovascular and peripheral vascular disease.
- Increases in serum cholesterol and blood glucose levels have been demonstrated
- Cardiovascular risks of all patients should be assessed and measures should be taken to reduce risks before starting and during treatment

Management of Chronic Myeloid Leukaemia Patients who are resistant or intolerant to Imatinib

Intolerance

- Patients who are intolerant of Imatinib should be treated with a second generation TKI, either Nilotinib, Dasatinib or Bosutinib. Availability of these drugs is limited by the terms of the Cancer Drugs Fund and an IFR may be required to access Dasatinib and Bosutinib. However, the availability of these agents is currently being reviewed by NHS England and more widespread use may be approved later in 2016.The choice of drug would be influenced by the nature of the intolerance to Imatinib, and other pre-morbid conditions as per resistant patients.

Sub-optimal response

The following describes a reasoned approach to the patient with a sub-optimal response:

- Consider compliance
- If the patient has achieved a complete cytogenetic response but not a major molecular response, consider continuing therapy at the current dose and monitoring closely. CCyR is the most important prognostic factor for progression free survival (PFS) and if the patient achieves a CCyR, overall survival (OS) and PFS are not affected by how long it takes to achieve.
- However, if CCyR has not been achieved by 18 months of therapy, consider a change of therapy.

Failure

- Patients failing Imatinib should receive a 2nd Generation tyrosine kinase inhibitor. Published efficacy data show little difference between the three licensed drugs, Nilotinib (at a dose of 400mg bd), Dasatinib and Bosutinib in this setting.

Factors that may influence choice are:

- Presence of a kinase domain mutation. This information will only be informative in minority of patients, where the presence of a so called 'gatekeeper' mutation will predict the response to one or other of the available TKIs. These are Y253H, E255K/V and F359C/V which will be resistant to Nilotinib, and F317L and V299L which will be resistant to Dasatinib. The T315I mutation is associated with resistance to all 2^{nd} G – TKIs as well as Imatinib and such patients should not be treated with these agents but will be eligible to receive Ponatinib via the CDF. They should also be assessed for allogeneic SCT in case of lack of response.
- Pre-morbid conditions.

The following table summarises the factors that may influence choice of one or other 2nd generation

TKI (after Laneuville, 2009): (Y = can use, N = No)

Co-morbidity	**Dasatinib**	**Nilotinib**	**Bosutinib**
Pancreatitis	Y	N	
Cardiovascular disease	Y	N	Y
Autoimmune disease	N	Y	Y
Dietary restriction	Y	N	Y
Post SCT	N	Y	Y
GI bleeding	N	Y	Y
Cardiac disease (arrhythmia, prolonged QTc)	Y	N	Y
Drug availability (NICE and NHS England)	N	Y	N

Management of CML in Pregnancy

There is little in the way of large published series about the management of chronic myeloid leukaemia in pregnancy.

The diagnosis of CML during pregnancy may be made more complicated as the physiological changes, including those in haematological parameters which accompany pregnancy, may mask the symptoms. The prothrombotic potential of a normal pregnancy is well recognized because of a physiological increase in haemostatic factors and prothrombotic proteins in addition to the physical obstruction of venous blood flow. As a result, thrombosis continues to be the most common cause of maternal morbidity and this may be compounded in the myeloproliferative diseases where there is an associated elevation in the platelet count.

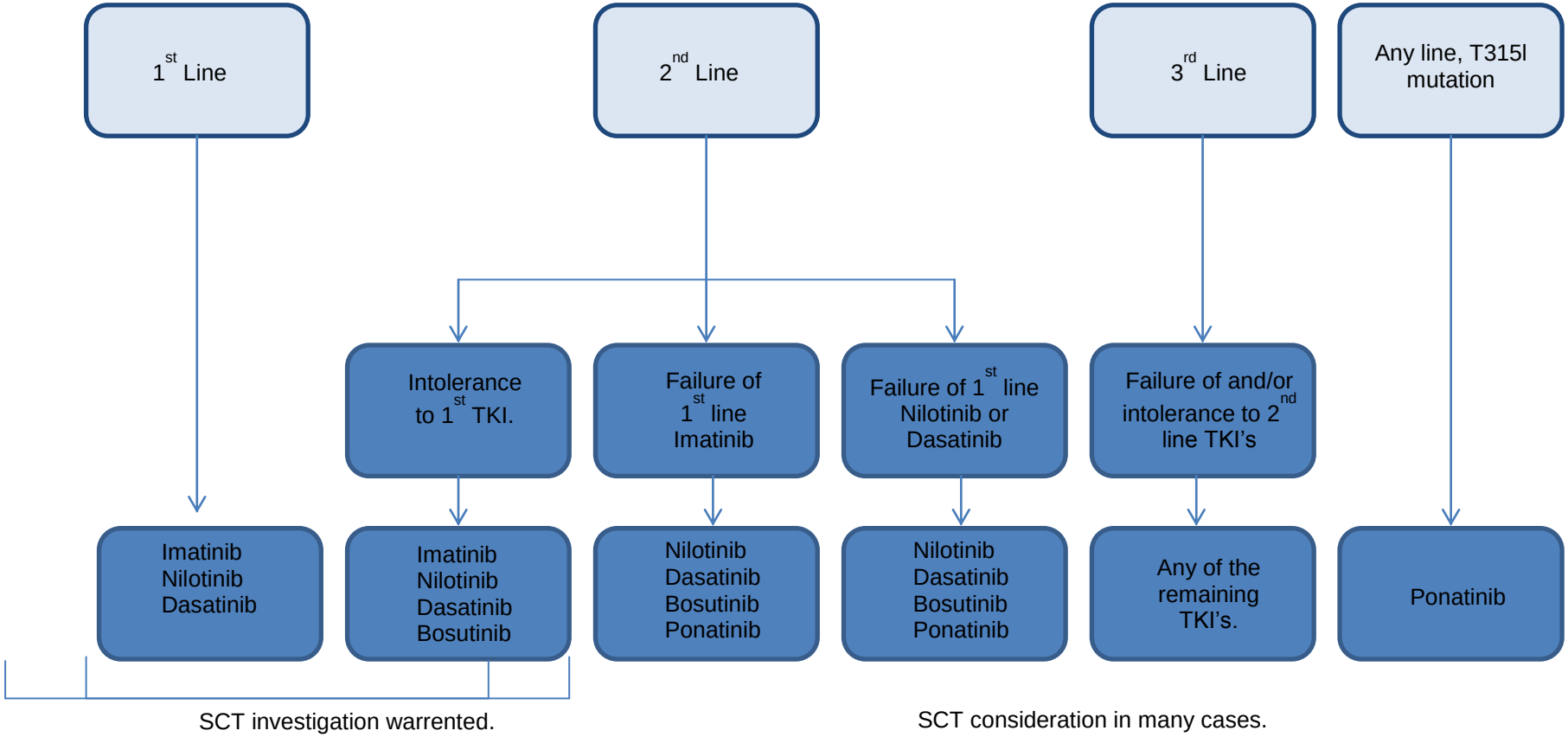
Therapeutic approaches for CML diagnosed in pregnancy have included supportive care in the form of leukapheresis, chemotherapy (Hydroxycarbamide [HC]), interferon-a (IFN-a), and Imatinib.

In cases where conception has occurred on Imatinib, Imatinib should be stopped and close monitoring of foetal development should be recommended, including a nuchal scan for foetal anomaly, regardless of maternal age. The parents should be informed of the known foetal potential risks and a judgment should be made according to the risk of transformation for the mother considering the existing disease response to therapy as effective treatment needs to be interrupted. Despite this recommendation, as Imatinib does not cross the placenta, some physicians have chosen to treat CML patients in pregnancy from the second trimester, and there are cases where Imatinib has not been discontinued upon conception.73 There is significantly less experience with 2G-TKIs (Bosutinib, Dasatinib, Nilotinib, and Ponatinib) in pregnancy.75 Dasatinib, a dual BCRABL/src kinase inhibitor crosses the placenta and leads to considerable levels in foetal plasma.81 In the first trimester, Dasatinib has been reported to cause foetal hydrops and severe foetal bicytopenia,76 but normal pregnancies have also been reported.

Bone Marrow Transplantation

- BMT remains an option for patients failing TKI therapy, but is rarely considered until the patient has failed sequential therapy with at least three TKIs. This should be discussed with the MDT lead.

Patient Pathway



Reference The Chronic Myeloid Leukaemia ESMO Clinical Practice Guideline, published 2017 – AN ONCOL (2017) 28(SUPPL4); IV41-IV51
Author: A.Hochhaus, S Saussele, G Rosti, F X. Mahon, J Janssen, H Jorth-Hansen, J Richtar & C Buske

3 PROCESS FOR MONITORING COMPLIANCE

Compliance will be audited within the MDT audit programme.

4 REFERENCES

- Hull and North Lincolnshire Haematology MDT operational policy September 2017.
- Haematological cancers: improving outcomes. NICE guideline [NG47] Published date: May 2016
- How I treat leukaemia during pregnancy Dragana Milojkovic and Jane F. Apperley Department of Haematology, Imperial College London, Hammersmith Hospital, London, United Kingdom. . (Blood. 2014;123(7):974-984
- The Chronic Myeloid Leukaemia ESMO Clinical Practice Guideline, published 2017 – AN ONCOL (2017) 28(SUPPL4); IV41-IV51 Author: A.Hochhaus, S Saussele, G Rosti, F X. Mahon, J Janssen, H Jorth-Hansen, J Richtar & C Buske

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