Pan Birmingham NHS
Cancer Network

Guideline for the Management of Patients with Chronic Myeloid Leukaemia (CML)

Version History

Version	Summary of change	Date Issued
3.0	Approved by Doug Wulff on behalf of the Governance Committee	14.11.08
3.1	Circulated at NSSG meeting,	14.02.11
3.2	Following NSSG with amendments by Fiona Clark	27.04.11
4.0	Endorsed by the Governance	10.05.11

Date Approved by Network Governance	**May 2011**

Date for Review	**May 2014**

Changes made during review in 2011

- **Change 1 –** nilotinib added as an alternative second line agent, in the setting of intolerance or resistance to imatinib.
- **Change 2** – dasatinib commercial preparations are changing to 80mg, 100mg and
- 140mg strength capsules, doses amended in this guideline accordingly.
- **Change 3** – Appendices added to inform on the European LeukaemiaNet

1. This guidance has been produced to support the following:

- The management of patients suspected of having CML
- The management of patients diagnosed with CML

2. Guideline Background

2.1 This document aims to combine up to date research, current thinking, and local expert opinion to generate Network Guidelines.

2.2 In Pan Birmingham Cancer Network two hospitals are designated transplant centres for haematological malignancies - University Hospital Birmingham Foundation Trust [UHBFT] and Heartlands Hospital (part of Heart of England Foundation Trust). These two hospitals treat patients with haematological malignancies at BCSH levels 1-4. In addition to this Good Hope Hospital (part of Heart of England NHS Foundation Trust) practices to level 1, Worcestershire Acute Hospital NHS Trust and Sandwell and West Birmingham Hospitals NHS Trust, Sandwell site practice to level 2.

2.3 The review of these guidelines has been brought forward to reflect the changes in clinical practice, in particular the increasing evidence for nilotinib in first and second line settings.

3. Guideline Statements

Referral

3.1 Patients with a combination of the following should undergo an urgent blood count and film ESR and plasma viscosity or C-reactive protein (+/- clotting screen):

- Fatigue
- Drenching night sweats
- Fever
- Weight loss
- Breathlessness
- Bruising / bleeding
- Recurrent infections
- Left upper quadrant pain
- Splenomegaly

4. Investigation and Diagnosis

4.1 Patients suspected of having chronic myeloid leukaemia should undergo the following:

a) Full blood count and manual differential WCC
b) Full clinical examination with documentation of liver and spleen size
c) Ultrasound of the abdomen for assessment of spleen size may also be required
d) Routine biochemistry to include U&Es, LFTs, calcium, LDH and uric acid levels
e) Bone marrow aspirate and trephine biopsy
f) Cytogenetics and assessment of presence of BCR-ABL transcripts by RT-PCR, on the marrow aspirate (or on peripheral blood)
g) For all patients the Hasford or New CML (Euro) score should be measured (see www.pharmacoepi.de.)

4.2 Marrow slides should be reported by a haematopathologist (histologist or haematologist) trained in leukaemia morphology. They should be reviewed by a second such consultant as quickly as possible and at the next available MDT meeting.

Primary Therapy

5. All Patients:

a) Should be discussed at the MDT prior to starting treatment.
b) Local, network and BCSH guidelines should be followed for the management of the following treatments and care:
    - Blood and blood product support
    - The use of growth factors
    - Neutropenia – prevention and treatment
c) Tumour lysis should be prevented by use of allopurinol and hydration to >3litres/day, intravenous fluids may be necessary for some patients. In advance of starting therapy, check electrolytes, creatinine and uric acid to identify patients at high risk of tumour lysis. Occasional patients may benefit from rasburicase at the start of treatment.
d) Therapeutic leucopheresis and buffy coat stem cell collection should be considered for patients with leucostasis e.g. deteriorating level of consciousness, papilloedema, retinal venous engorgement/haemorrhages, or priapism.
e) Bone marrow cytogenetics and quantitative RT-PCR should be repeated at 3 monthly intervals in patients treated with imatinib until patients achieve a complete cytogenetic remission (CCR) at which stage quantitation of BCR-ABL transcript numbers should be performed on peripheral blood at three monthly intervals indefinitely[3].
f) Should be considered for entry into National Institute for Health Research portfolio trials.

6. Patients in Chronic Phase (CP)

a) See section below on the role of stem cell transplantation in CML.
b) Where transplant is an option a buffy coat collection of cells should be considered.
c) Imatinib (400mg daily) should be used for initial cytoreductive therapy Patients starting imatinib should be monitored fortnightly for the first two months. It is important to be aware of the possibility of hepatotoxicity with imatinib as well as a number of possible drug interactions.
d) Clinicians should be aware of tumour lysis on starting therapy and advise on adequate hydration and allopurinol.
e) Other side effects which may be encountered include:

- Mild allergic type rashes, which may respond to simple anti-histamines.
- Severe dermatological reactions have been documented which may require steroid therapy or in some cases the discontinuation of Imatinib.
- Arthralgia which usually responds to simple treatment with non-steroidals.
- Fluid retention which usually manifests as peri-orbital oedema.

f) Imatinib should be stopped if either platelets fall below 50 x 10^9/L, or neutrophils fall below 1.0 x 10^9/L, and resumed once the counts recover to above these levels. If the count takes more than 2 weeks to return to these levels, consider dropping the dose to 300 mg daily. GCSF, administered once to three times a week may be useful to manage neutropenia. Dose reduction below 300 mg daily is rarely needed.

g) Up to 30% of newly diagnosed patients with CML in 1st chronic phase are intolerant or resistant to imatinib. Guidelines for defining imatinib resistance have been published by the European Leukemia Network (Appendix 1)[4] These have been widely adopted and provide a valuable set of criteria by which patients can be deemed to be imatinib resistant.[4]

h) Of note, nilotinib has been granted a licence for first line therapy as an alternative to imatinib.

6.1 Two second generation tyrosine kinase inhibitors; dastinib and nilotinib, are now available for the treatment of patients with imatinib resistance or intolerance. In younger patients allogeneic transplantation using an HLA identical sibling donor may also be considered.

6.2 Either dasatinib 100mg od or nilotinib 400mg bd may be instituted as second line therapy, for CML remaining in chronic phase, following intolerance to imatinib or resistance according to ELN criteria. The choice of second line agent should be based on patient characteristics, medical history and co-morbidities.. Principal side effects of the two agents from trials where they were used as second line agents are listed below:

Table III. Incidence (%) of treatment-related adverse events in patients exposed to second-line treatments for chronic-phase chronic myeloid leukemia.

	Imatinib 800 mg (n = 49)[55]		Dasatinib 70 mg BID (n = 101)[55]		Dasatinib 100 mg Once Daily (n = 165)[16]		Nilotinib 400 mg BID (n = 318)[17]	
Adverse Event	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Thrombocytopenia	NR	14	NR	57	NR	23	NR	28
Neutropenia	NR	39	NR	63	NR	36	NR	28
Anemia	NR	8	NR	20	NR	13	NR	8
Fluid retention	43	0	39	7	34	4	NR	NR
Superficial edema	43	0	20	1	18	0	NR	NR
Peripheral edema	NR	NR	NR	NR	3	0	11	0
Pleural effusion	0	0	25	5	18	2	NR	NR
Diarrhea	29	2	37	3	27	2	22	3
Fatigue	22	4	33	3	24	2	28	1
Headache	10	2	26	2	33	1	31	3
Nausea	33	0	24	0	18	1	31	1
Dyspnea	4	0	23	5	20	2	11	1
Rash	20	0	18	0	17	2	33	2
Pyrexia	10	0	14	0	5	1	14	1
Asthenia	4	0	15	0	NR	NR	14	0
Vomiting	24	0	10	0	7	1	21	<1
Pain in extremity (musculoskeletal pain)	12	2	21	1	19	2	13	1

NR = not reported.

From Brady Stein and B Douglas Smith, *Clinical Therapeutics* **32,** 5

6.3 Characterisation of abl kinase mutation status (see below) may be of importance in determining in future whether patients should receive dasatinib or nilotinib and should be performed on all patients with imatinib resistant CML. Specifically the presence of a T315I kinase domain mutation means that dasatinib and nilotinib treatment will not be effective and alternatives should be sought. Allogeneic stem cell transplantion is an important treatment for patients still in chronic phase who have failed treatment with imatinib and dasatinib.

7. Patients in Accelerated Phase (AP)

7.1 A number of definitions of accelerated phase are in existence but the criteria used by the International Bone Marrow Transplant Registry are:

a) White cell count (WCC) difficult to control with conventional use of busulphan or hydroxycarbamide.
b) Rapid doubling of WCC (<5 days).
c) 10% blasts in blood or marrow.
d) 20% blasts plus promyelocytes in blood or marrow.
e) 20% basophils plus eosinophils in blood.
f) Anaemia or thrombocytopenia unresponsive to busulphan or hydroxycarbamide.
g) Persistent thrombocytosis.
h) Additional chromosomal changes (evolving new clone). 80% of cases show
i) clonal evolution often with recognised chromosome abnormalities. (However, new subclones should be interpreted with caution as these may represent clonal selection by imatinib for partially resistant subclones, rather than clonal evolution linked to disease progression).
j) Increasing splenomegaly.
k) Development of chloromas or myelofibrosis.
l) Second (or subsequent) chronic phase after acute phase.

7.2 Patients fulfilling the criteria for accelerated phase disease should receive imatinib 600 mg daily. All patients with a suitable sibling or unrelated donor should be considered for allogeneic transplantation. Patients failing to respond to imatinib, should be treated with dasatinib 140mg od or nilotinib 400mg bd. Patients who fail to respond to dasatinib, or for whom that agent is contra-indicated (see above) should receive nilotinib 400 mg b.d.

8. Patients in Blast Crisis (BC)

8.1 It is important to determine whether patients have morphological features of a myeloid or lymphoid blast crisis. Patients who have developed blastic transformation whilst on imatinib would ordinarily have escalated their dose of imatinib to 800mg, so should therefore be considered for dasatinib 140mg once daily. Patients presenting in blast crisis should be commenced on dasatinib 140mg once daily. Patients who achieve a 2nd CP and have a suitable sibling or unrelated donor should be considered for an allogeneic transplant if they are under the age of 50 and fit enough to tolerate a myeloablative conditioning regimen. Allogeneic transplantation is not recommended in blastic transformation.

Patients with myeloid blast crisis may respond to induction regimens used in AML- there may be some benefit associated with the use of FLAG. ALL regimens (vincristine and prednisolone or UKALLXII) are valuable in treatment of lymphoid blast transformations. If allogeneic stem cell transplantation is contemplated it may be considered optimal practice, in patients with blast crisis, to elect to use standard

chemotherapy salvage regimens rather a second generation tyrosine kinase inhibitor.

9. Pregnancy

a) CML in pregnancy should be managed jointly between the haematologist and the obstetrician with full involvement of the mother.
b) Where appropriate consideration should be given to early induced labour.
c) It is desirable that some attempt to control the white cell count (and perhaps platelet count) in pregnancy should be attempted. Hydroxycarbamide is teratogenic in animals and one stillbirth and one malformed infant have been reported after exposure in pregnancy. It should generally be avoided.
d) Alternative treatments include α-interferon, which has been well documented as being safe in the management of CML in pregnancy, and leucopheresis. This is the most common therapeutic manoeuvre cited in the literature with good control of the white cell count and a successful outcome for mother and baby in all reported cases.

9.1 Based on the published evidence, a reasonable recommendation for the management of CML in <u>first chronic phase</u> diagnosed in pregnancy would be as follows:

a) Initial leucopheresis to control the white cell count, together with allopurinol and aspirin therapy, especially if there is associated thrombocytosis.
b) Instigation of α-interferon therapy to maximum tolerated dose to control the white cell count with intermittent leucopheresis to keep the white cell count below 20 $x10^9$/l and platelets below 400 $x10^9$/l until delivery.
c) No particular precautions need to be taken at delivery, assuming stable peripheral blood parameters, and normal vaginal delivery should be possible.
d) Patients presenting in AP or BC may require treatment that is toxic to the foetus including imatinib. This needs to be managed and options discussed (including termination of the pregnancy) on an individual basis.

10. Transplantation

10.1 Allogeneic SCT remains the only curative therapy in CML. Although up-front treatment with imatinib has become the preferred option in the great majority of patients with newly diagnosed chronic phase CML, allogeneic transplantation using a sibling or unrelated donor remains an important therapeutic option in:

a) Patients intolerant of imatinib, nilotinib and dasatinib
b) Patients with a sub-optimal response to imatinib, nilotinib or dasatinib
c) Patients who have lost a haematological, cytogenetic or molecular response achieved with imatinib, nilotinib or dasatinib.
d) Patients with accelerated phase CML.

10.2 In young patients with an available sibling donor there may be a role for up-front transplantation in a small number of patients.

10.3 Reduced intensity allografts have increased the age at which allogeneic transplants can be performed and there is growing evidence that they have an important role in the management of older patients with CML who are resistant or intolerant to tyrosine kinase inhibitors.

11. Patient Information and Counselling

11.1 All patients, and with their consent, their partners will be given access to appropriate written information during their investigation and treatment, and on diagnosis will be given the opportunity to discuss their management with a Clinical Nurse Specialist who is a member of the relevant Multi Disciplinary Team. The patient should have a method of access to the Haematology team at all times.

11.2 Access to psychological support will be available if required. All patients should undergo a Holistic Needs Assessment and onward referral as required.

12. Clinical Trials

12.1 Wherever possible, patients who are eligible should be offered the opportunity to participate in National Institute for Health Research portfolio clinical trials and other well designed studies.

12.2 Where a study is only open at one Trust in the Network, patients should be referred for trial entry. A list of studies available at each Trust is available from Pan Birmingham Cancer Research Network. Email: PBCRN@westmidlands.nhs.uk .

12.3 Patients who have been recruited into a clinical trial will be followed up as defined in the protocol.

13. Follow-up

13.1 Follow-up should be in the haematology clinics at regular intervals, usually 6 weekly although patients require more careful monitoring immediately after the commencement of imatinib (see above). Patients who have been recruited into a clinical trial will be followed up as per the protocol. Response to imatinib should be monitored initially by three monthly bone marrow aspirates to confirm acquisition of a CCR. In patients who have achieved a CCR with imatinib evidence of continued response should be documented by three monthly quantitation of BCR-ABL transcript numbers in peripheral blood. If the BCR-ABL transcript number is rising the test should be repeated urgently and if evidence of loss of response confirmed a

bone marrow aspirate and search for kinase domain mutations should be performed. Patients should be advised to report promptly to their GP for an urgent FBC if they develop any signs or symptoms that might indicate disease relapse.

14. Palliative Care

Early links should be made to the palliative care team where the treatment intent is not curative or where the patient has symptoms that are difficult to manage.

Monitoring of the Guideline

Implementation of the guidance will be considered as a topic for audit by the NSSG in 2012\2013.

References

1 www.bcshguidelines.com
2 NICE 2005 Referral Guidelines for Suspected Cancer www.nice.org.uk
3 Recommendations for the Management of BCR-ABL-positive Chronic Myeloid Leukaemia (2007) BCSH: www.bcshguidelines.com
4 Baccarani M, Saglio G, Goldman J, Hochhaus A, Simonsson B, Appelbaum F, et al. Evolving concepts in the management of chronic myeloid leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet. Blood. 2006 Sep 15;108(6):1809-20.

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Approval Signatures

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Appendix 1 - Response Criteria

(as per European LeukemiaNet expert guidance*: Blood 2006 108(6) 1809*:Baccarani et al)

Table 8. Response definition and monitoring

	Hematologic response	Cytogenetic response	Molecular response (BCR-ABL to control gene ratio according to the International scale)
Definitions	Complete: Platelet count < 450 × 10^9/L; WBC count < 10 × 10^9/L; differential without immature granulocytes and with less than 5% basophils; nonpalpable spleen	Complete: Ph^+ 0% Partial: Ph^+ 1%-35% Minor: Ph^+ 36%-65% Minimal: Ph^+ 66%-95% None: Ph^+ > 95%	"Complete" indicates transcript nonquantifiable and nondetectable Major: ≤ 0.10
Monitoring	Check every 2 wk until complete response achieved and confirmed, then every 3 mo unless otherwise required	Check at least every 6 mo until complete response achieved and confirmed, hence at least every 12 mo	Check every 3 mo; mutational analysis in case of failure, suboptimal response, or transcript level increase

Complete HR, complete CgR, and major MolR should be confirmed on 2 subsequent occasions. CgR is evaluated by morphologic cytogenetics of at least 20 marrow metaphases. FISH of peripheral blood cells should be used only if marrow cells cannot be obtained. MolR is assessed on peripheral blood cells. The International scale for measuring MolR is that proposed by Hughes et al.[189]

Table 9. Operational definition of failure and suboptimal response for previously untreated patients in ECP CML who are treated with 400 mg IM daily

Time	Failure	Suboptimal response	Warnings
Diagnosis	NA	NA	High risk, del9q+, ACAs in Ph^+ cells
3 mo after diagnosis	No HR (stable disease or disease progression)	Less than CHR	NA
6 mo after diagnosis	Less than CHR, no CgR (Ph^+ > 95%)	Less than PCgR (Ph^+ > 35%)	NA
12 mo after diagnosis	Less than PCgR (Ph^+ > 35%)	Less than CCgR	Less than MMolR
18 mo after diagnosis	Less than CCgR	Less than MMolR	NA
Anytime	Loss of CHR*, loss of CCgR†, mutation‡	ACA in Ph^+ cells§, loss of MMolR§, mutation‖	Any rise in transcript level; other chromosome abnormalities in Ph^- cells

Failure implies that the patient should be moved to other treatments whenever available. Suboptimal response implies that the patient may still have a substantial benefit from continuing IM treatment but that the long-term outcome is not likely to be optimal, so the patient becomes eligible for other treatments. Warnings imply that the patient should be monitored very carefully and may become eligible for other treatments. The same definitions can be used to define the response after IM dose escalation. For risk definitions refer to Table 2. For mutations refer to Table 5. For the definition of HR, CgR, and MolR, refer to Table 8.

PCgR indicates partial CgR; and NA, not applicable.

*To be confirmed on 2 occasions unless associated with progression to AP/BC.

†To be confirmed on 2 occasions, unless associated with CHR loss or progression to AP/BC.

‡High level of insensitivity to IM.

§To be confirmed on 2 occasions, unless associated with CHR or CCgR loss.

‖Low level of insensitivity to IM.