



# Haematology Cancer Clinical Guidelines

Haematology Expert Advisory Group (EAG)  
on behalf of Northern Cancer Alliance

<b>Title:</b>	Haematology Cancer Clinical Guidelines
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**Document Control**

Version	Date	Summary	Review Date
V17			

**Date Agreed:** Haematology EAG members agreed the Guidelines on:  
Emailed to group on 12.04.18 for formal endorsement at the next meeting.

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## **SECTION 7**

# **GUIDELINES FOR THE MANAGEMENT OF CHRONIC MYELOID LEUKAEMIA**

Where \*\* indicated, please see notes overleaf

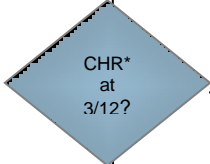
# Suspected

**Investigations\*.**  
**Define phase of disease.** (see table)  
**Document 'disease risk' data.** Sokal: age, spleen size, platelet count, blasts. (Extras for Hasford: basos, eos)  
**Consider consent** for data capture and research samples – work in progress

**Initial management.** If typical CML morphology and WBC >50x10<sup>9</sup>/L then start treatment whilst definitive diagnosis awaited. Perfectly reasonable to start HU whilst Ph and/or BCR-ABL status awaited.  
**Start definitive treatment.** Once diagnosis confirmed by BM Ph or BCR-ABL **please consider the SPIRIT 2 trial for all patients before starting imatinib.** ([www.spirit-cml.org/spirit-2-home.aspx](http://www.spirit-cml.org/spirit-2-home.aspx))\*.  
 In non-trial patients: imatinib 400mg (CP), 600mg (AP/BP) daily.  
 Allopurinol at individual discretion but rarely required for more than one month. No necessity to use hydroxyurea rather than imatinib initially but HU can be used pending definitive diagnosis. Very few, if any, patients should be allografted 'up front'. Leucopheresis not essential but useful for research or if transplant might be considered.

3 months. Response assessment.  
 FBC. PCR EVERY 3/12\*

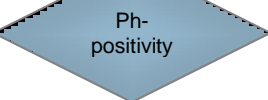
**Who to refer/discuss?\*** Consider: possible SPIRIT trial patients; patients under 50 to discuss potential allograft strategy; advanced disease at presentation or on treatment; drug resistance and/or difficult patients; use of 2<sup>nd</sup> generation TKI drugs; difficult toxicity; children (rare); pregnancy.



No

Yes

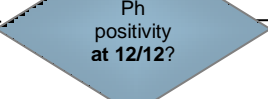
6 months. Response assessment  
 Bone marrow cytogenetics, PCR\*



0% (CCR\*)

>95%

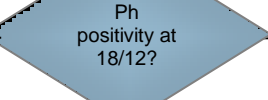
1-95%: continue treatment



0% (CCR\*)

>35% (i.e. NO MCR\*)

<=35% (MCR\*)



0% (CCR\*)

>0% (i.e. NO CCR\*)

0% (CCR\*)

3 monthly PCR.  
 No further BMs unless loss of response.

Continue imatinib



No

Yes

Mutation analysis.  
 Consider alternative therapy: 2<sup>nd</sup> generation TKI\* or transplant.  
 (Consider repeat BM if loss of response)

**\*NOTES**

This algorithm is based on evidence from the IRIS/0106 trial which has been described and referenced in more detail in the European Leukaemia Net and forthcoming BCSH guidelines documents. The tables below are modified from these documents and the reader is referred to these sources for further detail.

**Investigations at diagnosis.** FBC, differential esp. blast %, biochem screen inc. LFTs, urate.

Bone marrow (or blood if BM difficult) for cytogenetics or PCR for BCR-ABL. Trephine not necessary. There is no absolute requirement to perform a BM examination. At individual discretion the diagnosis can be made on PCR detection of BCR-ABL alone but baseline marrow may be useful for future comparison and to define additional chromosomal abnormalities.

**Possible additional investigations.** HLA type patient and any sibs if less than 60.

**Monitoring. FBC** (look out for early neutropenia and thrombocytopenia (10-15%) on imatinib 400mg); **LFTs** probably at every visit - occasional patients develop late liver tox (1-2 years+ out); **bone marrow cytogenetics, PCR and mutation testing** as per algorithm.

**Loss of response.** *Obvious:* loss of CHR or significant increase in BM Ph (e.g. 10% @6/12, 80% at 12/12). *More subtle:* Failure to achieve MMR (<0.1% BCR-ABL/ABL ratio) or sustained increase in previously low PCR result. See table below for ELN summary – by no means ‘set in stone’ as yet, a work in progress.

**Managing toxicity** is beyond the scope of this document, please contact Anne or Steve to discuss.

**Samples. PCR for BCR-ABL:** 2.5 ml in PAXgene™. Send to Molecular Pathology Service, Department of Haematology, RVI, Newcastle NE1 4LP. Contact details below.

**ABL tyrosine kinase domain mutation analysis** (available Autumn 2007): same as PCR sample and send to the same address. PCR and mutation analysis can be done on same sample if need be. Samples can be sent by 1<sup>st</sup> class post, courier or taxi as you wish. If posting, please avoid posting on thursdays/fridays as samples likely to languish over the weekend and be useless. Sample ‘freshness’ important: to arrive within 24 hours if possible. Please discuss with Steve O’Brien or Andy Hall before dispatch of samples.

**Contacts**

*Clinical advice & PCR, mutation interpretation* Steve O’Brien: 0191 282 0605, 07789 200525, [s.g.o'brien@ncl.ac.uk](mailto:s.g.o'brien@ncl.ac.uk)  
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*SPIRIT-2* Wendy Banks 0191 282 0904 [wendy.banks@ncl.ac.uk](mailto:wendy.banks@ncl.ac.uk)

**2<sup>nd</sup> generation Tyrosine Kinase Inhibitors (TKIs)**

Nilotinib 400 mg twice daily or Dasatinib 100mg daily, is standard dose. *NOTE: dasatinib and nilotinib don't work against the T315I mutation.* Nilotinib use is approved by NICE and dasatinib should be used only in cases of nilotinib intolerance

Bosutinib (SKI606), MK0457 (T315I inhibitor) and others not available as yet.

Definitions of response to treatment

Haematological response (HR)	Cytogenetic response (CR)	Molecular response (MR)
Complete (CHR)	Complete (CCR)	Complete (CMR)
Platelets <450 x 10 <sup>9</sup> /L WBC <10 x 19 <sup>9</sup> /L Differential: No immature granulocytes and <5% basophils	Partial Major (MCR) is combination of complete and partial Minor Minimal No cytogenetic response	Major (MMR)
	0% Ph-positive metaphases or BCR-ABL FISH positivity 1-35% 36-65% 66-95% >95%	No detectable BCR-ABL transcripts <0.1% BCR-ABL to ABL ratio (Sample must be of good quality and have adequate ABL)

Definitions of failure or sub-optimal response to imatinib based on ELN guidelines				Phase of disease. Based on European Leukemia Net guidelines, not WHO.		
Time	Failure	Suboptimal response	Warnings	Chronic phase	Accelerated phase	Blast phase/crisis
Diagnosis	'Warnings' at diagnosis: high risk (Sokal/Hasford); del 9q+; additional chromosome abnormalities in Ph-positive cells.					
3 months	No HR	No CHR	-	None of the criteria for AP or BP have been met	Blast cells 15-29% in PB or BM	Blast cells ≥30% in PB or BM
6 months	No CHR No CR	No MCR	-	Additional cytogenetic abnormalities alone do not indicate accelerated phase	Blast cells plus promyelocytes in PB or BM >30%, with blast cells <30%	Extramedullary blast involvement
12 months	No MCR	No CCR	No MMR		Basophils in blood >20%	
18 months	No CCR	No MMR	-		Persistent thrombocytopenia (<100 X 10 <sup>9</sup> /L) unrelated to therapy	
Any time	Loss of CHR Loss of CCR Mutation (ie T315I)	Chromosomal abnormalities in Ph+ cells Loss of MMR Mutation	Any rise in PCR level Chromosome abnormalities in Ph-negative cells			