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Pan-London Haemato-Oncology Clinical Guidelines

Acute Leukaemias and Myeloid Neoplasms
Part 3: Chronic Myeloid Leukaemia

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Contents

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Disclaimer

These guidelines should be read in conjunction with the latest NICE guidance, and all applicable national/international guidance. The prescribing information in these guidelines is for health professionals only. It is not intended to replace consultation with the Haematology Consultant at the patient's specialist centre. For information on cautions, contra-indications and side effects, refer to the up-to-date prescribing information. While great care has been taken to see that the information in these guidelines is accurate, the user is advised to check the doses and regimens carefully and if there is any uncertainty about the guidance provided, you should discuss your queries with a Haematology Consultant or Senior Pharmacist. No set of guidelines can cover all variations required for specific patient circumstances. It is the responsibility of the healthcare practitioners using them to adapt them for safe use within their institutions and for the individual needs of patients.

Contact us

The writing cycle for the guidelines will be from May-July each year. If you wish to be part of the writing group, please contact us through the following link: Pan London Blood Cancer (or via uclh.panlondonbloodcancer@nhs.net).

If you wish to report errors or omissions that require urgent attention please contact us via the same email addresses.

1 Introduction

> *This guidance should be read in conjunction with the European Leukaemia Net (ELN) guidelines on chronic myeloid leukaemia (Baccarani, et al, 2013).*

Chronic myeloid leukaemia (CML) is a clonal myeloproliferative neoplasm (MPN) originating from the pluripotent haematopoietic stem cell in which cells of the myeloid lineage undergo inappropriate clonal expansion caused by a molecular lesion. The characteristic genetic abnormality of CML, the Philadelphia chromosome, results from a reciprocal translocation of genetic material on the long arms of chromosome 9 (ch9) and chromosome 22 (ch22), t(9;22)(q34;q11).

The abnormal ch22 was first observed in Philadelphia – hence the common terminology, Philadelphia (Ph) chromosome – but the reciprocal translocation of ch9 was not recognised until 1973. t(9;22) results in the juxtaposition of the human analogue of the v-ABL oncogene from ch9 with the BCR housekeeping gene on ch22 to produce the fusion BCR-ABL1 gene. This is transcribed into the fusion BCR-ABL1 mRNA, and translated into the Bcr-Abl1 protein, a constitutively activated tyrosine kinase (TK). This leads to eventual replacement of all myeloid tissue by differentiating leukaemia cells. The disease typically progresses through three distinct phases – chronic, accelerated and blast crisis – during which the leukaemic clone progressively loses its ability to differentiate.

The worldwide annual incidence of CML is 1–1.5 cases per 100,000 population, with the incidence being slightly higher in males. It accounts for 15–20% of all leukaemia cases in adults in the Western world. Although the disease may occur at any age, the median age at presentation is between 50 and 60 years. A higher incidence of CML was noted among people who were exposed to large doses of radiation following the nuclear explosions at Hiroshima and Nagasaki. There is no recognised familial influence, and no causal association between CML and industrial chemicals or alkylating agents has been demonstrated.

Before the development of targeted therapy with tyrosine kinase inhibitors (TKIs), the median survival was 5–7 years. The TKIs have profoundly affected outcome and hence prevalence: current predictions suggest that in the USA prevalence will rise from 70,000 in 2010, to 112,000 in 2020, and then plateau at 181,000 in 2050.

At diagnosis, the Ph chromosome is detected by conventional methods in approximately 95% of CML cases. The remaining cases have either variant translocations involving a third, and sometimes fourth, chromosome or cryptic translocations. In these cases, routine cytogenetic analysis is unable to detect the Ph chromosome, and the diagnosis relies on demonstration of the fusion transcript by either fluorescence in situ hybridisation (FISH) or real-time quantitative polymerase chain reaction (RT-qPCR).

The molecular consequence of t(9;22)(q34;q11) is the generation of a gene that is expressed as a BCR-ABL1 RNA transcript translated into a 210-kd protein known as p210BCR-ABL. The p210BCR-ABL oncoprotein functions as a constitutively active TK that can phosphorylate a number of cytoplasmic substrates with other activities, leading to alterations in cell proliferation, differentiation, adhesion and survival.[1, 2] The leukaemic clone in CML has a tendency to acquire additional oncogenic mutations over time, usually associated with progression to accelerated phases of disease or resistance to TKIs. At the chromosomal level, changes include

amplification/duplication of t(9;22), trisomy 8, trisomy 19, and abnormalities of chromosome 17. At the molecular level, mutations in the kinase domain of BCR-ABL account for about 50% of imatinib resistance in patients with CML in chronic phase, and 80% of advanced phases cases.[2]

CML is triphasic: the great majority of patients present in the 'chronic phase' (CP) where the symptoms can be relatively easily controlled. But without effective therapeutic intervention, patients will progress through a period of increasing instability known as the 'accelerated phase' (AP), to a terminal transformation to 'blast crisis' (BC) which resembles acute leukaemia.

2 Referral Pathways from Primary Care

Patients with a high WBC or platelet count and/or suspected CML should be referred to a haematologist for assessment as soon as possible through immediate referral.

All new patients should be referred to the multidisciplinary team (MDT) for confirmation of diagnosis, prognosis and management plan, taking into account their performance status, needs and co-morbidities. A joint approach with elderly care physicians and palliative care teams may be appropriate, depending on the phase of the disease.

The following patients should be brought to the MDT:

- All new patients with chronic myeloid leukaemia (CML) in order to confirm the diagnosis and treatment plan.
- All patients where a new line of therapy needs to be considered.
- All patients with a restaging assessment of response to treatment with a tyrosine kinase inhibitor (TKI) at three, six and 12 months if warning signs are present/failure of response (see European LeukaemiaNet (ELN) 2013 guidelines and section 7: Treatment, Table 7).
- All patients in whom an allogeneic stem cell transplant is a consideration.
- All patients where a trial of Treatment free remission is to be attempted

Information to be captured and documented prior to, or during, the MDT should include:

- demographic information
- referring physician and/or GP
- performance status
- an indicator of co-morbidities (e.g. co-morbidity score)
- any relevant history, including cardiovascular co-morbidities
- pertinent positive and negative findings on physical examination (splenomegaly, etc.)
- spleen size (by ultrasound if needed, based on body habitus)
- FBC, peripheral blasts, haematinics, LFTs, U&E, LDH, urate, transfusions
- bone marrow aspirate +/- trephine histology
- bone marrow aspirate, immunophenotyping of blasts

- cytogenetic status for t(9;22) and any additional clonal abnormalities
- FISH for BCR-ABL for rapid confirmation of diagnosis if required
- RT-qPCR for BCR-ABL1 (if available)
- specific diagnosis/phase of CML
- other relevant imaging
- risk score (Sokal +/- EUTOS/ELTS score)
- availability of a clinical trial/research study and whether the patient is eligible
- management and treatment plan
- key worker/clinical nurse specialist (CNS)
- named consultant or treating team
- for follow-up: cumulative result of BCR-ABL, including the BCR-ABL at three months; results of the most recent bone marrow aspirate and cytogenetics; co-morbidities; and relevant side effects on TKI. A repeat trephine is not required routinely for follow-up marrows, and should be performed according to clinical requirements. Routine bone marrows at set time-points are not required, and are performed according to clinical indication (e.g. difficulty in interpreting RT-qPCR response, new cytopenia/macrocytosis).

The MDT outcome form should be sent to the GP (by email or preferably fax) within 24 working hours of the MDT discussion as per Peer Review Guidance.

2.1 Treatment location

Patients with CML can be managed at a BCSH (British Committee for Standards in Haematology) Level 1 facility. Patients may be referred to centres with specific expertise, or which have available trials. Biobanking of diagnostic material may be considered if appropriate approvals (ethics/R&D permission) are in place at the referring site.

2.2 Centres with specialist CML expertise

The following patients must be referred to a CML centre:

- Management protocols for adults contemplating parenthood or for women during pregnancy are more complex and individualised. These patients should be discussed with a consultant who is experienced in such cases and the patient may be referred to sub-specialist centres, e.g. for obstetric care and/or allogeneic stem cell transplant
- Failure of 2G-TKI
- Failure of first-line TKI
- Advanced phase disease (accelerated and blast phase)
- Patients being considered for a treatment-free remission (TFR).

Patients who fail to respond, lose response or experience disease progression may be discussed with a sub-specialist centre, especially if they progress through second-line treatment.

Patients considered for stem cell transplantation need management at a JACIE-accredited centre.

3 Investigation and Diagnosis

Patients with persistent, unexplained, raised neutrophil counts should be referred to a specialist centre for a blood film, peripheral blood cytogenetics and/or molecular investigation, and proceed to a bone marrow investigation if needed.

Chronic myeloid leukaemia (CML) presents in the chronic phase (CP) in about 90% of patients. Between 20% and 40% of individuals in whom CP-CML is diagnosed are asymptomatic and are discovered incidentally. This is increasingly common due to the expansion of routine health screening.

Common non-specific symptoms at presentation include fatigue, night sweats, weight loss and spontaneous bruising or bleeding, and are normally due to hypercatabolic symptoms, splenomegaly (detected in 50–90% of patients at diagnosis), splenic infarction, anaemia or platelet dysfunction (Table 1).

Males with very high white blood cell (WBC) counts rarely present with leucostasis-related priapism. The features of advanced phase CML are those of cytopenia (including bleeding), splenic enlargement and general cachexia. The characteristic clinical finding is splenomegaly.

The clinical suspicion of CML dictates a series of investigations (Table 2), the most important of which are the blood count with morphological examination, bone marrow aspirate with an accurate differential, cytogenetics for all chromosomal abnormalities including t(9;22), and reverse transcriptase polymerase chain reaction (RT-qPCR) for the BCR-ABL1 fusion mRNA. Cytogenetic analysis occasionally fails for technical reasons, in which case the BCR-ABL1 fusion gene can be identified by fluorescent in situ hybridisation (FISH), using specific chromosome markers. In a small proportion of cases the BCR-ABL1 fusion gene can be present without t(9;22) being detectable by conventional cytogenetics and in this situation can be identified by FISH and/or RT-qPCR.

In the peripheral blood, neutrophilia and immature circulating myeloid cells are hallmark features of CML. More than 50% of patients present with a WBC count >100 x 10^9/L, with blasts usually accounting for <2% of the WBCs. Absolute basophilia is invariably present, and eosinophilia is common. The marrow in chronic phase CML is hypercellular and typically shows myeloid hyperplasia and an elevated myeloid to erythroid ratio. Maturation of precursors is normal and dysplastic features are not routinely found.

The quickest way to confirm a suspected case of CML is to detect in the peripheral blood the presence of either the Philadelphia (Ph) chromosome or the chimeric transcripts of the BCR-ABL fusion gene. The Ph chromosome can be identified by metaphase cytogenetics or FISH, while the presence of the BCR–ABL1 fusion gene may be confirmed by RT-qPCR carried out on peripheral blood-derived RNA. Quantification of BCR-ABL at diagnosis is important for monitoring of minimal residual disease in patients undergoing therapy, and it therefore essential to determine the transcript type at presentation. Both FISH and RT-qPCR can detect cryptic chromosomal translocations, whereas FISH has the advantage of identifying unusual variant rearrangements that are outside the regions amplified by the RT-qPCR primers. Although both assays confirm the diagnosis of CML, a marrow evaluation is mandatory in order to rule out advanced-stage disease and is also required to detect the presence of additional chromosomal abnormalities. Definitions of CML-CP, accelerated phase (AP) and blast phase/blast crisis (BP/BC) are summarised in Table 3. There are many classifications, including from the World Health Organization (WHO); the ELN

2013 classification has been used by all major studies with tyrosine kinase inhibitor (TKI) and is therefore backed by data. The ELN 2013 classification is preferred.

Table 1: Presenting features of CML

FREQUENT

- Fatigue
- Night sweats
- Malaise and weight loss
- Left upper quadrant pain/discomfort/satiety
- Splenomegaly

LESS FREQUENT

- Priapism
- Retinal haemorrhages
- Thrombosis and/or bleeding
- Bone pain*
- Hepatomegaly
- Lymphadenopathy*
- Skin infiltration*
- Extramedullary mass (chloroma)*

* Suggestive of advanced-phase disease.

The following investigations should be performed at diagnosis:

- Full history including occupational exposure to potential carcinogens and family history.
- Identification of potential sibling donor for those patients who are potential transplant candidates only.
- Physical examination including size of liver and spleen below the costal margins, height and weight.
- Routine biochemistry to include U&Es, LFTs, calcium, LDH and urate.
- Full blood and manual differential.
- HBsAg, HBcAb
- Bone marrow aspirate +/- trephine (BMAT) – samples for cytogenetics.
- Immunophenotyping of peripheral blood and BM if AP or BC.
- Peripheral blood RT-qPCR analysis for BCR-ABL transcript type.
- Lumbar puncture and cytospin/cytology/immunophenotyping are indicated if lymphoid/mixed phenotype BC is confirmed. This may be delayed until routine intrathecal chemotherapy if clinically appropriate.
- Consider fertility issues if patient is of reproductive age.
- Assessment of cardiovascular risk factors (triglycerides, cholesterol, blood pressure, glucose and HbA1c) if treatment is likely to aggravate CV disease

- All newly diagnosed patients should have a Sokal +/- EUTOS/ELTS score.

3.1 Fertility

Consideration of fertility preservation should be made for those of reproductive age.

3.1.1 Onco-fertility expertise

Semen cryopreservation should be considered for all male patients. Current data suggest that imatinib does not affect fertility and that male patients can safely conceive while taking imatinib. Data for men taking alternative TKIs are limited or absent. In addition, it is currently not possible to predict individuals at high risk of progression and who might require high-dose therapy. For this reason, men who wish to preserve their fertility should be encouraged to bank sperm.

For young patients with CML with advanced or complex disease who are due to undergo AML induction-type chemotherapy and/or an alloSCT, the options for fertility preservation should be discussed and the patient referred to a fertility specialist for preservation of sperm, ovarian tissue or fertilised embryos.

Management protocols for adults contemplating parenthood or for women during pregnancy are more complex and individualised. These patients should be discussed with a consultant experienced in such cases.

Table 2: Mandatory diagnostic tests for CML

Blood count with blood film differential. This will typically show a ‘left shift’ of the myeloid series with the presence of immature myelocytes and metamyelocytes, basophils and eosinophils. These must be accurately quantified as the results contribute to accurate identification of disease stage and prognostic scoring systems.
Bone marrow aspirate with differential to include percentages of blasts, promyelocytes, myelocytes, eosinophils and basophils.
Cytogenetics and karyotyping by G banding. FISH is not sufficient at diagnosis as it is unable to identify chromosomal abnormalities in addition to the t(9;22) translocation.
Reverse transcriptase quantitative polymerase chain reaction (RT-qPCR) for BCR-ABL1 mRNA transcripts.

This extensive work-up confirms the diagnosis, but also facilitates disease staging and prognostic scoring. The definitions of AP and BC are largely dependent on the proportion of blasts in the blood and bone marrow but vary in the two commonly used systems (WHO and European LeukaemiaNet (ELN)) (Table 3). Direct comparison of studies using the differing criteria is difficult and is further compounded in the field of transplantation by their use of yet another definition set. However, the majority of the recent TKI studies have adopted the ELN criteria and continue to do so..

If the patient is a potential transplant candidate and leukapheresis is being considered, ensure virology tests are documented, as is standard practice. If allogeneic HSCT is being considered, perform HLA typing of patient and siblings, and consider a volunteer unrelated donor (VUD) search.

Table 3: Criteria for the definition of AP and BP, as recommended by the ELN and WHO[4]

Phase of disease	Definition	
	ELN criteria	**WHO criteria**
Accelerated phase	• Blasts in blood or marrow 15–29%, or blasts plus promyelocytes in blood or marrow >30%, with blasts <30% • Basophils in blood ≥20% • Persistent thrombocytopenia (<100 × 10^9/L) unrelated to therapy • Clonal chromosome abnormalities in Ph+ cells (CCA/Ph+*), major route, on treatment	• Blasts in blood or marrow 10–19% • Basophils in blood ≥20% • Persistent thrombocytopenia (<100 × 10^9/L) unrelated to therapy • CCA/Ph+* on treatment • Thrombocytosis (>1000 × 10^9/L) unresponsive to therapy • Increasing spleen size and increasing WBC count unresponsive to therapy
Blast phase/crisis	• Blasts in blood or marrow ≥30% • Extramedullary blast proliferation, apart from spleen	• Blasts in blood or marrow ≥20% • Extramedullary blast proliferation, apart from spleen • Large foci or clusters of blasts in the bone marrow biopsy

* CCA/Ph+ = clonal chromosome abnormalities in Ph+ cells.

The ELN criteria were used in all main studies of TKI. The use of TKI may require a change of the boundaries between CP, AP and BP/BC and modify to some extent the classic subdivision of CML in three phases, but the data are not yet sufficient for a revision.

3.2 Pathology

Careful attention must be paid to the labelling of forms and samples before sending to the Specialist Integrated Haematological Malignancy Diagnostic Service (SIHMDS). Samples are unlikely to be processed unless clearly and correctly labelled.

BMAT:

- slides for morphology to SIHMDS lab
- 2–5ml in EDTA for immunophenotyping with a slide if indicated
- 2–5ml in heparin (PFH or lithium heparin) for cytogenetics/FISH
- trephine for histopathology if indicated.

3.3 Imaging

Patients may have an ultrasound of the abdomen performed at diagnosis to document spleen (and liver) size, and thereafter when clinically appropriate. Clinical examination of the abdomen is however usually sufficient.

4 Risk Stratification

Within the chronic phase (CP), certain features of the presenting blood count and differential, together with age and spleen size, are used in scoring systems for the prediction of survival (Table 4). The Sokal and Hasford scores were developed for patients treated with busulfan and interferon-alpha, respectively, and continue to have value in the tyrosine kinase inhibitor (TKI) era; the more recent EUTOS (European Treatment Outcome Study) score, derived from TKI-treated patients, is simpler and has been shown to be of value in at least one large study.

ELTS: The EUTOS long-term survival (ELTS) score subsequently also evaluated prognosis by specifically examining the probability of dying of CML, defined as death after disease progression. This latest score showed greater age, number of peripheral blood blasts, larger spleen size and low platelet counts indicated a greater risk of dying of CML and established a new long-term survival score with three prognostic groups.

Table 4: Scoring systems validated for parameters at diagnosis for treatment with busulfan (Sokal), interferon (Hasford) and imatinib (EUTOS)

Parameter	Sokal	Hasford	ELTS	EUTOS
Age	0.116 × (age – 43.4)	0.666 when >50 y	0.0025 x (age in completed years/10)3	
Spleen (cm below costal margin)	0.0345 × (spleen size – 7.51)	0.042 × spleen size	+ 0.0615 x spleen size	4 × spleen
Platelets × 10^9/L	0.188 × [(plts /700)^2 – 0.563]	1.0956 when >1,500	+ 0.4104 x (platelet count/1000)-0.5	
PB basophils %	Not included	0.20399 when >3%	Not included	7 × %
PB eosinophils %	Not included	0.0413 × %	Not included	
PB blasts	0.087 (blasts % – 2.1)	0.0584 x blast %	+ 0.1052 x blasts in peripheral blood	
Low risk	<0.8	≤780	≤ 1.5680	≤87
Intermediate risk	0.8–1.2	781–480	> 1.5680 but ≤ 2.2185	
High risk	>1.2	>1,480	> 2.2185	>87

Table 5: Calculation of relative risk

Study	Calculation	Risk definition by calculation
Sokal, *et al*., 1984[3]	Exp 0.0116 × (age – 43.4) + 0.0345 × (spleen – 7.51) + 0.188 × [(platelet count ÷ 700)^2 –0.563] + 0.0887 × (blast cells – 2.10)	Low risk: <0.8 Intermediate risk: 0.8–1.2 High risk: >1.2

Euro Hasford, *et al*., 1998[4]	0.666 when age ≥50 y + (0.042 × spleen) + 1.0956 when platelet count >1,500 × 10^9/L + (0.0584 × blast cells) + 0.20399 when basophils >3% 1 (0.0413 × eosinophils) × 100	Low risk: ≤780 Intermediate risk: 781–1,480 High risk: >1,480
EUTOS Hasford, *et al*., 2011[5]	Spleen × 4 + basophils × 7	Low risk: ≤87 High risk: >87

The sum of both Sokal and Hasford can be correlated with the following risk groups:

Prognosis	Hasford score	Sokal score
Good	≤780	<0.8
Moderate	>780–≤1,480	0.8–1.2
Poor	>1,480	>1.2

Online calculators

Sokal and Hasford: www.leukemia-net.org/content/leukemias/cml/euro__and_sokal_score/index_eng.html

EUTOS: www.leukemia-net.org/content/leukemias/cml/eutos_score/index_eng.html

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

5 Management of Disease and Treatment-related Complications

Also see section 8: Supportive Care.

5.1 Hyperviscosity syndrome

Urgent platelet apheresis or leukapheresis can be undertaken if high counts are causing symptoms of hyperviscosity, including priapism and visual disturbance. Cytoreductive therapy must be initiated or optimised simultaneously. If the clinical situation is urgent and leukapheresis cannot be arranged in a timely manner, venesection of a single unit of blood might be indicated after discussion with a sub-specialist.

5.2 Hyperuricaemia

Patients should be treated with allopurinol or rasburicase if clinically indicated, and according to local protocols and patient-specific factors (e.g. renal failure, WBC count, level of LDH/uric acid). All patients should be well hydrated and receive allopurinol 100–300mg daily (depending on renal function) until achieve CHR in order to avoid symptoms of gout and other complications.

5.3 Management of haematological adverse events (chronic phase)

Adverse events	Management
Neutropenia	Hold therapy if grade ≥3 until ANC ≥1.0 Restart at lower dose if second occurrence

	Consider G-CSF if recurrent/persistent, or sepsis
Thrombocytopenia	Hold therapy if platelets <50 × 10^9/L until ≥75 × 10^9/L Restart at lower dose if second occurrence
Anaemia	Treatment interruption/dose reduction usually not indicated Consider erythropoietin or darbepoetin alfa

5.4 Management of haematological adverse events (advanced phases)

Adverse events	Management
Neutropenia	Hold therapy if grade ≥4 and unrelated to disease Restart once ANC ≥1.0 Restart at lower dose if second occurrence
Thrombocytopenia	Hold therapy if platelets <10 × 10^9/L and unrelated to disease Restart once platelets ≥20 × 10^9/L Restart at lower dose if second occurrence
Anaemia	Treatment interruption/dose reduction usually not indicated

5.5 Management of non-haematological adverse events

Adverse events	Management
Skin rash	Symptomatic therapy (e.g. antihistamines); topical steroids; occasionally systemic steroids (prednisolone 0.5–1mg/kg)
Elevated transaminases	Grade 1 or 2: monitor Grade 3: interrupt therapy; consider restart a lower dose when recovered/switch TKI;0.5–1mg/kg prednisolone can be of benefit
Elevated bilirubin	Grade 1 or 2: monitor Grade 3: interrupt; restart a lower dose when recovered to grade ≤1 Elevation of bilirubin common with nilotinib, particularly among patients with Gilbert syndrome; in those instances, may allow continuation of therapy in some instances with grade 3
Hyperglycaemia	More common with nilotinib Stop therapy if grade ≥3; restart therapy when recovered to grade ≤1 with reduced dose No contraindication to use nilotinib in patients with diabetes mellitus ; if nilotinib mandatory, close monitoring and adjustment of hypoglycaemic agents as needed
Muscle cramps	Magnesium glycerophosphate or magnesium oxide or calcium carbonate may sometimes help Electrolyte replacement if needed (e.g. potassium, calcium, magnesium) Consider quinine sulphate
Arthralgia, bone pain	Routine pain relief the intensity of the pain declines with time
Peripheral oedema	Diuretics as needed (usually furosemide)
Nausea and vomiting	Take imatinib with food Anti-emetics if necessary
Diarrhoea	Loperamide
Periorbital oedema	Consider dose adjustment (diuretics are of minimal benefit)

6 Patient Information/Support

If the diagnosis of CML is certain, patients should be informed that CML is a clonal disorder that is considered malignant. Their prognosis based on response to treatment (achievement of a complete cytogenetic response (CCyR)) should be discussed, along with possible treatment options.

All patients must have access to a key worker. This is usually (but not always) the clinical nurse specialist.

The clinical nurse specialist should ensure that all patients are offered a Holistic Needs Assessment (HNA) at key pathway points, including within 31 days of diagnosis, at the end of each treatment regime, and whenever a person requests one. Following each HNA, every patient should be offered a written care plan. This plan should be developed with the patient and communicated to all appropriate healthcare and allied healthcare professionals.

Written and verbal information is essential and the key worker/clinical nurse specialist plays a key role in ensuring that patients have access to appropriate and relevant written information about their condition.

The Bloodwise CML information booklet, International CML Foundation and Macmillan Cancer Support information websites are good sources of patient information at diagnosis and can be downloaded from the websites below:

https://bloodwise.org.uk/sites/default/files/documents/CML_patient_info_booklet.pdf

www.cml-foundation.org

https://www.macmillan.org.uk/information-and-support/leukaemia/leukaemia-chronic-myeloid

https://www.leukaemiacare.org.uk/

Patients should have access to supportive care information and rehabilitation throughout the cancer pathway. Consider referral to the appropriate services, including rehabilitation, when indicated.

7 Treatment

See Annex 1 for TKI drug interactions.

> *Formal written consent should be obtained for all patients before starting any cytoreductive therapy.*

https://www.cancerresearchuk.org/health-professional/treatment-and-other-post-diagnosis-issues/consent-forms-for-sact-systemic-anti-cancer-therapy#sact_conset6

7.1 Chronic phase

7.1.1 General considerations

Initial treatment with a TKI has become the gold standard for patients who present in the CP, and a CCyR (Table 6) is considered to be the minimum acceptable response, since it translates into improved transformation-free survival (TFS). Around 70% of patients achieve CCyR after frontline treatment with imatinib,[6, 7] and the eight-year probability of being in continuing CCyR while still taking imatinib or a second-line treatment with a second-generation TKI is 77%.[8]

In randomised trials of nilotinib and dasatinib versus imatinib, a higher rate of CCyR has been reported in patients treated with first-line second-generation TKIs (80% vs 65% at 12 months), with a significantly lower rate of transformation to AP or BP with nilotinib (2.1–3.2% vs 6.7%, respectively).[9] However, the benefit of each drug has been considered in isolation, without accounting for the effect of subsequent therapy.

Patients treated with TKIs should be monitored closely to assess their response and to detect resistance. BCR–ABL1 transcript numbers in the blood should be regularly measured according to ELN recommendations. The achievement of a major molecular response (MMR or MR^3) (Table 6) has been shown to be associated with a reduced risk of loss of CCyR.

In patients who lose CCyR on imatinib, a kinase domain (KD) mutation analysis should be performed and a second-generation TKI introduced without delay. Second-generation TKIs (2G-TKI) induce CCyR in approximately 50% of patients who are resistant to imatinib.[10,11] Useful responses have also been identified using the third-generation agent ponatinib in patients who have failed a 2G-TKI. Approximately 40% of patients will achieve CCyR: this figure is higher if the indication for ponatinib is the identification of the T315I mutation as the cause of TKI resistance.[12]

Patients who fail to respond to treatment with available TKIs should be considered for treatment with allogeneic stem cell transplant (AlloSCT), providing they can tolerate the procedure and have a donor. AlloSCT carries a significant risk of morbidity and mortality, but is curative for most patients who survive the procedure.[13]

7.1.2 First-line treatment

Emergency cytoreduction

Hydroxycarbamide and allopurinol should be initiated if the WBC is elevated (e.g. ≥100 × 10^9/L), to reduce WBC counts and to minimise complications associated with tumour lysis. A usual dose would be 2–4g daily but this may need to be adjusted according to patient need.

Imatinib, dasatinib and nilotinib are approved by the National Institute for Health and Care Excellence (NICE) for first-line treatment of patients with chronic phase CML. Parameters to take into consideration for the choice of first-line TKI include the Sokal score, co-morbidities and patient choice. Patients with high-risk Sokal scores, or with major route clonal chromosome abnormalities (CCA) at diagnosis should have consideration of HLA-typing if considered fit for an AlloSCT. 2G-TKI might be preferred for these patients as it has been shown to reduce the risk of CML progression, particularly in patients defined as high risk by the Sokal score.

All patients should have a BCR-ABL transcript analysis before the start of treatment to identify the nature of the BCR-ABL breakpoint. After starting TKI therapy, patients should have their BCR-ABL transcript level monitored three months after the start of treatment. Those who have not achieved an early molecular response on imatinib (i.e. BCR-ABL >10% IS) might be considered for second-line treatment with a second-, or third-generation TKI; for those who started on front-line nilotinib or dasatinib, there are no clear data or guidelines regarding the best course of action.[8, 14, 15]

7.1.3 Second-line and subsequent line treatment

Patients who are intolerant to the first-line TKI should be considered for an alternative TKI approved as first- or second-line treatment.

Patients who meet ELN 2013 criteria for failure on imatinib (Table 7 and Table 8) should have HLA-typing (together with their siblings) if appropriate, a KD mutation analysis and be started on a second-generation TKI (dasatinib, nilotinib or bosutinib). The choice of second-line TKI depends on co-morbidities and the finding of a KD mutation. Patients who have developed a T315I KD mutation should be treated with ponatinib, following a cardiovascular risk assessment.

Sequencing TKIs for intolerance and a good response continues according to patient tolerability. Third line treatment for resistance should be discussed with a specialist CML centre.

Asciminib is a first in class novel allosteric inhibitor targeting the myristoyl pocket of BCR-ABL and is a highly selective BCR-ABL inhibitor. The activity of Asciminib is not affected by mutations in the ATP binding pocket, and thereby is effective against the T315I mutation. Asciminib is available through clinical trials and on a named patient basis.

7.1.4 Advanced phase

For patients presenting in blastic transformation and who have not previously been treated with imatinib, transient haematologic remission rates are 50–70%, with cytogenetic response rates of 12–17%. Ideally, patients should be entered into a clinical trial.

For de-novo blast crisis, management should take place with a 2G-TKI upfront in combination with intensive chemotherapy (usually Flag-Ida), if clinically appropriate.

If blastic transformation evolves during imatinib, treatment with dasatinib/ponatinib combined with intensive chemotherapy (i.e. for acute myeloid leukaemia/acute lymphoblastic leukaemia) should be given. Dasatinib has been shown to cross the blood–brain barrier.[16] Consideration should also be given to the administration of intrathecal therapy which is necessary in lymphoid/mixed phenotype blast crisis.

Responses to TKIs are transient in blast crisis, therefore, if a return to CP ('second' CP)has been achieved, all patients should proceed to an alloSCT if appropriate and if a donor has been identified, regardless of excellent molecular responses.[17] Two courses of chemotherapy are given (without TKI interruption if feasible) prior to allo-SCT.

Patients with de novo accelerated phase should be treated up-front with a 2G-TKI and considered for alloSCT unless they achieve an optimal response with TKIs. Patients with secondary accelerated phase (that evolves after TKI failure in CP), should be managed like blastic transformation if appropriate.

Treatment-free remission considerations for the optimal responder

Discontinuation of TKI is an option for a select group of patients who have responded optimally to therapy and achieved CMR4, alternatively known as a deep molecular response (DMR). Evidence for this approach comes from a number of trials worldwide that have employed specific eligibility criteria with strict molecular monitoring on a frequent basis to ensure patient safety. Following treatment discontinuation, roughly two thirds of patients are able to remain off therapy.

Halving the standard dose of TKI for 12 months before withdrawing therapy completely shows a higher recurrence free survival rate (RFS) rate of 76% at 24 months for those patients in stable MR4, but also highlights the premise that patients in MMR only should not undergo treatment discontinuation.

The majority of recurrences occur within 6 months of discontinuation but later molecular recurrence after a number of years has also been noted emphasising the need for ongoing molecular monitoring.

A proportion of patients have experienced a TKI withdrawal syndrome, predominantly musculoskeletal pain, that has required pain relief, rheumatological review, and a short course of low dose steroids. The risks and benefits of a treatment-free remission (TFR) attempt should be carefully discussed with the patient and subsequently in the regional MDT, or with a CML specialist. TFR should only be attempted if the below criteria are met:

- It is recommended that any patient considering discontinuation should be discussed at the local MDT or at least with the regional CML specialist
- First CP CML only (no previous history of AP/BC)
- TKI treatment for at least 3 years, optimally 5 years
- Known and quantifiable typical BCR-ABL1 transcript (e13a2/e14a2)
- CMR 4 (<0.01% IS) for 2 years, 4 consecutive RT-qPCR results, 3 months apart
- No resistance to any TKI, or detection of an Abl kinase domain mutation
- Reliable RT-qPCR test, sensitivity of detection of >MR4.5 on IS, and results provided in no less than 2 weeks

- Four-weekly molecular monitoring for first 6 months, 6-weekly for the next 6 months, 2-monthly for year 2, 3-monthly thereafter
- Prompt resumption of TKI (ideally full dose/or MTD) on confirmed loss of MMR; monthly RT-qPCR until MMR regained; Abl kinase domain mutation testing if no MMR in 6 months.

Table 6: Conventional definitions of cytogenetic and molecular responses to treatment for chronic myeloid leukaemia[18]

Ph-positive marrow metaphases (%)	**Designation**
0	Complete cytogenetic response (CCyR)
1–35	Partial cytogenetic response (PCyR)
36–95	Minor cytogenetic response
>95	None
Percentages cited above are based on a minimum of 20 analysable metaphases. Complete and partial responses are often grouped together as major cytogenetic responses (MCyR).	
Ratio of BCR-ABL to ABL (%)	**Designation**[18]
≤0.1% BCR-ABL^{IS}	Major molecular response (MMR or MR^{3})
Detectable disease ≤0.01% BCR-ABL^{IS} or undetectable disease in cDNA with ≥10,000 ABL transcripts	MR^{4}
Detectable disease ≤0.0032% BCR-ABL^{IS} or undetectable disease within cDNA with ≥32,000 ABL transcripts	MR$^{4.5}$
It is generally accepted that CCyR corresponds to an approximate 2-log reduction in transcript levels or 1% on the international scale. MMR is usually defined as a 3-log reduction in transcript levels or 0.1% on the international scale (IS).	

Table 7: Definition of response to first-line TKI[19]

	Optimal	**Warning**	**Failure**
Baseline	N/A	High risk or *CCA/Ph+, major route	N/A
3 months	BCR-ABL1 ^{IS}≤10% and/or Ph+ ≤35%	BCR-ABL1 ^{IS} >10% and/or Ph+ 36–95%	Non-CHR and/or Ph+ >95%
6 months	BCR-ABL1^{IS} <1% and/or Ph+ 0	BCR-ABL1 1 ^{IS} –10% and/or Ph+ 1–35%	BCR-ABL1 ^{IS} >10% and/or Ph+ >35%
12 months	BCR-ABL1 ^{IS} ≤0.1%	BCR-ABL1 ^{IS} >0.1–1%	BCR-ABL1 ^{IS} >1% and/or Ph+ >0
Then, and at any time	BCR-ABL1 ^{IS} ≤0.1%	**CCA/Ph- (-7, or 7q-)	Loss of CHR Loss of CCyR Confirmed loss of MMR^{+} Mutations CCA/Ph+

* CCA/Ph+: clonal chromosome abnormalities in Ph+ cells.
** CCA/Ph-: clonal chromosome abnormalities in Ph- cells.

Table 8: Definition of response to second-line TKI[19]

	Optimal	Warning	Failure
Baseline	N/A	No CHR or loss of CHR on imatinib or lack of CyR to first-line TKI or high risk	N/A
3 months	BCR-ABL1 ^{IS} ≤10% and/or Ph+ <65%	BCR-ABL1 >10% and/or Ph+ 65–95%	No CHR or Ph+ >95% or new mutations
6 months	BCR-ABL1 ^{IS} ≤10% and/or Ph+ <35%	Ph+ 35–65%	BCR-ABL1 ^{IS} >10% and/or Ph+ >65% and/or new mutations
12 months	BCR-ABL1 ^{IS} <1% and/or Ph+ 0	BCR-ABL1 ^{IS} 1–10% and/or Ph+ 1–35%	BCR-ABL1 ^{IS} >10% and/or Ph+ >35% and/or new mutations
Then, and at any time	BCR-ABL1 ≤0.1%	*CCA/Ph- (-7, or 7q-) or BCR-ABL1 ^{IS} >0.1%	Loss of CHR or loss of CCyR or PCyR New mutations Confirmed loss of MMR^{+} Mutations CCA/Ph+

* In two consecutive tests.

8 Supportive Care

8.1 Anaemia

Red cell transfusions should be administered only if required in addition to dose-modification of TKI or cytoreductive medication(s). Erythropoietin can be of therapeutic benefit. Other causes of anaemia should be considered.

8.2 Haemostasis and thrombosis

For thrombotic events, anti-coagulate as per local protocols and ensure counts are well controlled to prevent future events.

8.3 Hyperviscosity syndrome

Urgent leukapheresis can be undertaken if high counts are causing symptoms of hyperviscosity. TKI and/or cytoreductive therapy must be initiated or optimised simultaneously. It would be clinically appropriate to transfer a patient with a very high white cell count to a centre than can offer urgent leucapheresis even if the patient asymptomatic at presentation.

8.4 Infection

Local protocols should be followed for treatment of infections and prophylaxis.

8.5 Pain management

For symptomatic splenomegaly (now rare), consider hydroxycarbamide versus other chemotherapy, surgery or splenic irradiation.

9 Treatment Summary and Care Plan

The MDT outcome form and clinic letters will serve to communicate new lines of treatment with the GP.

As most TKIs are administered lifelong, patients with CML are followed for life by a haematologist experienced in such disorders.

Treatment summaries should therefore be agreed when there are any significant changes in treatment and follow-up plans. Holistic Needs Assessments (HNAs) should be offered through follow-up, with a care plan completed to document the plans to address the issues raised by the patient.

There are two related but distinct documents which patients should be given when there are changes in treatment.

- A **treatment summary** provides a summary of the cancer treatments received by the end of the first treatment, planned follow-ups (including mechanisms for these), and signs and symptoms of which to be aware. Their aim is to provide information not only to the patient, but also to the GP about possible consequences of cancer and its treatment, signs of recurrence and other important information.
- A **care plan** is generated as a result of an HNA and is the agreed plan between the patient and healthcare professional about how the identified areas of concern will be addressed. This may cover provision of information (e.g. through an information prescription), onward referral for specialist assessment and intervention (e.g. breathlessness management), or

things which the patient themselves can do (e.g. contact their HR department about graduated return to work options).

10 Follow-up Arrangements

Patients who start on TKI should initially have 1-2 weekly FBC, U&Es, LFTs and clinical review, usually for the first month. Once FBC is within normal range the clinic visits can be adjusted. All patients on treatment should attend 3–4 monthly clinic appointments with FBC, U&Es, LFTs and BCR-ABL quantification by RT-qPCR, when they achieve MMR. Patients on treatment in long-standing complete molecular response could be seen 4–6 monthly.

All patients should be monitored by
RT-qPCR (peripheral blood) for the determination of BCR-ABL transcript level which is indicative of response. A bone marrow aspirate with cytogenetics +/- trephine should be considered every 3 months for patients who meet the ELN 2013 criteria of failure and in whom it is appropriate to do so (i.e. based on performance status and age/risk stratification). All patients should be monitored by RT-qPCR (peripheral blood) for the determination of BCR-ABL transcript level which is indicative of response. Routine bone marrow surveillance is not indicated. If there is concern regarding unexplained cytopenia then bone marrow should be considered to exclude progression/Ph neg cytogenetic abnormalities (sMDS) or other pathology.

Patients who have achieved an MMR/MR^3 should be monitored every 3 months by peripheral blood RT-qPCR.

Patients may have shared care between a specialist site and the local treating hospital; these arrangements must be clearly outlined so that the patient is clear where to attend in an emergency and understands the lines of communication between the sites.

11 End-of-life Care

For older patients, in particular those with high-risk disease, discussions with regards to prognosis and treatment options should also include discussions on end-of-life care. These are to facilitate transitions between active disease-modifying therapy to clinical trials, or supportive care only at the time of disease progression/non-response.

The named CNS, patient, family members and palliative care teams, as well as members of the inpatient ward team, may be involved. Clear documentation of the discussion with guidance to the treating teams is helpful in communicating these discussions and outputs to the wider team that may care for the individual.

12 Data Requirements

Accurate data collection is essential to monitor outcomes, and the collection of this information, particularly clinical data, remains the responsibility of the members of the multidisciplinary team with support from a data manager. Haematology services are required to submit data to nationally mandated datasets for all patients diagnosed with haematological cancer.

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Annex 1: Tyrosine Kinase Inhibitor Drug Interactions

Detailed drug interaction with imatinib, dasatinib and nilotinib can be found in the publication by Haouala, *et al.* (*Blood*, 2011).

IMATINIB

Imatinib is metabolised mainly by CYP isoenzyme 3A4, whereas CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A5 are reported to play a minor role in its metabolism. This TKI has also been shown to be a substrate of hOCT1, Pgp, and BCRP. The metabolites of imatinib are eliminated predominantly through biliary excretion.

Active substances that may increase imatinib plasma concentrations:

Substances that inhibit the cytochrome P450 isoenzyme CYP3A4 activity (e.g. ketoconazole, itraconazole, erythromycin, clarithromycin) could decrease metabolism and increase imatinib concentrations. Caution should be taken when administering imatinib with inhibitors of the CYP3A4 family.

Active substances that may decrease imatinib plasma concentrations:

Substances that are inducers of CYP3A4 activity could increase metabolism and decrease imatinib plasma concentrations. Co-medications which induce CYP3A4 (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital, fosphenytoin, primidone or Hypericum perforatum, also known as St John's wort) may significantly reduce exposure to imatinib, potentially increasing the risk of therapeutic failure and should be avoided.

Active substances that may have their plasma concentration altered by imatinib:

Caution is recommended when administering imatinib with CYP3A4 substrates with a narrow therapeutic window (e.g. cyclosporin or pimozide). Imatinib may increase the plasma concentration of other CYP3A4 metabolised drugs (e.g. triazolo-benzodiazepines, dihydropyridine calcium channel blockers, certain HMG-CoA reductase inhibitors, i.e. statins, etc.).

- Warfarin is metabolised by CYP2C9; patients who require anti-coagulation should have INR monitored more carefully.
- *In vitro*, imatinib inhibits the cytochrome P450 isoenzyme CYP2D6 activity at concentrations similar to those that affect CYP3A4 activity. Imatinib at 400 mg twice daily had an inhibitory effect on CYP2D6-mediated metoprolol metabolism. Dose adjustments do not seem to be necessary when imatinib is co-administrated with CYP2D6 substrates; however, caution is advised for CYP2D6 substrates with a narrow therapeutic window such as metoprolol. In patients treated with metoprolol, clinical monitoring should be considered.
- Clinical cases of hypothyroidism have been reported in thyroidectomy patients undergoing levothyroxine replacement during treatment with imatinib. TSH levels should be closely monitored in such patients as the plasma exposure to levothyroxine may be decreased when imatinib is co-administered.

- Metabolism of imatinib is mainly hepatic, and only 13% of excretion is through the kidneys. In patients with hepatic dysfunction (mild, moderate or severe), peripheral blood counts and liver enzymes should be carefully monitored. Cases of liver injury, including hepatic failure and hepatic necrosis, have been observed with imatinib.
- *In vitro*, imatinib inhibits paracetamol O-glucuronidation. Caution should therefore be exercised when using imatinib and paracetamol concomitantly, especially with high doses of paracetamol. Paracetamol may be taken, but not at the maximum daily dose.
- In Ph+ ALL patients, there is clinical experience of co-administering imatinib with chemotherapy, but drug–drug interactions between imatinib and chemotherapy regimens are not well characterised. Imatinib adverse events, i.e. hepatotoxicity, myelosuppression or others, may increase and it has been reported that concomitant use with L-asparaginase could be associated with increased hepatotoxicity.

DASATINIB

Dasatinib is metabolised in an active derivative and other inactive metabolites by the CYP3A4 isoenzyme and was also reported to be a substrate of BCRP and Pgp. Dasatinib has an inhibitory activity against CYP2C8 and CYP3A4. Plasma protein binding is around 96% for dasatinib, mainly to albumin.

Active substances that may increase dasatinib plasma concentrations:

Potent inhibitors of CYP3A4 (e.g. ketoconazole, itraconazole, erythromycin, clarithromycin, ritonavir, telithromycin) will increase serum levels of dasatinib.

Active substances that may decrease dasatinib plasma concentrations:

- Potent CYP3A4-inducers (e.g. rifampicin, dexamethasone, phenytoin, carbamazepine, St John’s wort) will decrease serum levels of dasatinib.
- Long-term suppression of gastric acid secretion by H2-blockers or proton pump inhibitors is likely to reduce serum levels of dasatinib.

BOSUTINIB

Active substances that may increase bosutinib plasma concentrations:

The concomitant use of bosutinib with potent or moderate CYP3A-inhibitors should be avoided, as an increase in bosutinib plasma concentration will occur. Selection of an alternate concomitant medicinal product with no or minimal CYP3A inhibition potential, if possible, is recommended. If a potent or moderate CYP3A-inhibitor must be administered during bosutinib treatment, an interruption of bosutinib therapy or a dose reduction in bosutinib should be considered.

Active substances that may decrease bosutinib plasma concentrations:

The concomitant use of bosutinib with potent or moderate CYP3A-inducers should be avoided as a decrease in bosutinib plasma concentration will occur.

NILOTINIB

Nilotinib undergoes metabolism by CYP3A4. It is also a substrate of the efflux transporter BCRP.9,23. Nilotinib is known to inhibit CYP2C8, CYP2C9, CYP2D6, CYP3A4, UGT1A1 and Pgp. Drugs that strongly inhibit CYP3A4 (e.g. ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin and ritonavir) can increase nilotinib levels and should not be administered concurrently. Grapefruit juice and any other foods that are known CYP3A4-inhibitors should also be avoided.

In patients taking CYP3A4-inducers (e.g. phenytoin, rifampicin, carbamazepine, phenobarbital and St John's wort), alternative agents with less enzyme induction should be considered.

Nilotinib is a competitive inhibitor of CYP3A4, CYP2C8, CYP2C9 and CYP2D6 *in vitro*, potentially increasing the concentrations of drugs eliminated by these enzymes. Since warfarin is metabolised by CYP2C9 and CYP3A4, it should be given with caution. Other medications for anti-coagulation should be considered.

In vitro data suggest that nilotinib has the potential to prolong cardiac ventricular repolarisation (QT interval) and therefore caution should be exercised when co-administering other drugs that can lead to QT prolongation, e.g. macrolide antibiotics, chlorpromazine, fluoxetine, levofloxacin.

Nilotinib should be used with caution in patients who have or may develop prolongation of QT. These include patients with hypokalaemia or hypomagnesaemia, patients with congenital long QT syndrome, patients taking anti-arrhythmic medicines (such as amiodarone, disopyramide, procainamide, quinidine and sotalol) or other drugs that lead to QT prolongation (such as chloroquine, halofantrine, clarithromycin, haloperidol and methadone) and cumulative high-dose anthracycline therapy.

Nilotinib capsules contain lactose. Nilotinib is therefore not recommended for patients with rare hereditary problems of galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption. Nilotinib should also be used with caution in patients with diabetes mellitus, as hyperglycaemia can occur in more than 50% of patients.

PONATINIB

Ponatinib is metabolised by CYP3A4. Caution should be exercised with concurrent use of ponatinib and moderate or strong CYP3A-inhibitors such as atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, voriconazole and grapefruit juice.

Caution should be exercised with concurrent use of ponatinib and strong CYP3A-inducers such as carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin and St John's wort, which may decrease ponatinib serum concentrations.

Medicinal products that elevate the gastric pH (such as proton pump inhibitors, H2-blockers or antacids) may decrease the solubility of ponatinib and subsequently reduce its bioavailability.

Ponatinib may have the potential to increase plasma concentrations of co-administered substrates of Pgp (e.g. digoxin, dabigatran, colchicine, pravastatin) or BCRP (e.g. methotrexate, rosuvastatin, sulfasalazine) and may increase their therapeutic effect and adverse reactions. Close clinical surveillance is recommended when ponatinib is administered.

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