LCA Haemato-Oncology Clinical Guidelines

Acute Leukaemias and Myeloid Neoplasms

Part 3: Chronic Myeloid Leukaemia

April 2015
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Appendices
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 present 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 (RQ-PCR).

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. 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.
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 medical intervention, they will progress through a period of increasing instability known as the ‘accelerated phase’ (AP), to terminal transformation to an acute leukaemic-like illness, or ‘blast crisis’ (BC).
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, via a 2 week wait pathway (see Appendix 1: 2 Week Wait Referral Forms).

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 (see Annex 7). 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 Leukaemia Net 2013 guidelines and section 7: Treatment, Table 7).
- All patients in whom an allogeneic stem cell transplant is a consideration.

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 and 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
- specific diagnosis/phase of CML
- other relevant imaging
- risk score (Sokal or Hasford)
- 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 for follow-up marrows.

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

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 (see section 12: Research/Clinical Trials). Biobanking of diagnostic material may be considered if appropriate approvals (ethics/R&D permission) are in place at the referring site; alternatively patients may be referred directly. The available facilities are:

**Imperial College Healthcare NHS Trust**
- Biobanking Service
- John Goldman Centre for Cellular Therapy
- Hammersmith Hospital
- 150 Du Cane Road
- London W12 0NN

**King's College Hospital NHS Foundation Trust**
- Haematology Tissue Bank
- Rayne Institute
- 123 Coldharbour Lane
- London SE5 9NU

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.

Referral pathways to CML centres in the LCA are:

**Imperial College Healthcare NHS Trust**
- Professor Jane Apperley or Dr Dragana Milojkovic
- Department of Haematology
- Hammersmith Hospital Campus
- 150 Du Cane Road
- London W12 0NN
- Tel: 020 8383 3237
- Email: j.apperley@imperial.ac.uk or d.milojkovic@imperial.ac.uk
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 (see Annex 5).
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 leukostasis-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. Cytogenetics 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: 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 10⁹/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 RQ-PCR 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. 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 RQ-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 classification by Kantarjian and colleagues has been used by all major studies with tyrosine kinase inhibitor (TKI) and is therefore backed by data.
Table 1: Presenting features of CML

<table>
<thead>
<tr>
<th>FREQUENT</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fatigue</td>
<td>Night sweats</td>
</tr>
<tr>
<td></td>
<td>Malaise and weight loss</td>
<td>Left upper quadrant pain/discomfort/satiety</td>
</tr>
<tr>
<td></td>
<td>Splenomegaly</td>
<td></td>
</tr>
</tbody>
</table>

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 tree.
- Identification of potential sibling donor.
- Physical examination including size of liver and spleen below the costal margins, height and weight.
- Ultrasound of the abdomen to document spleen size.
- Routine biochemistry to include U&Es, LFTs, calcium, LDH and urate.
- Full blood count and manual differential.
- HIV, HBV, HCV, CMV, EBV.
- Bone marrow aspirate and trephine (BMAT) – samples for cytogenetics/molecular (BCR-ABL).
- Immunophenotyping of peripheral blood and BM if AP or BC.
- Peripheral blood RT-PCR analysis for BCR-ABL transcripts.
- Lumbar puncture and cytospin/cytology/immunophenotyping are indicated if BC is confirmed.
- Consider fertility issues if patient is of reproductive age.
- Assessment of cardiovascular risk factors (triglycerides, cholesterol, blood pressure, glucose and HbA1c).
- All newly diagnosed patients should have a Hasford/Sokal or new CML (Euro) score.
3.1. Fertility

Consideration of fertility preservation should be made for those of reproductive age (men below the age of 55 and women below the age of 40). Please see the LCA guidance and recommendations for referral to fertility services for more information on referral criteria and contact details for services.

3.1.1. Onco-fertility expertise

Expert onco-fertility advice should be considered in line with the LCA guidance.

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

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood count with blood film differential</td>
<td>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.</td>
</tr>
<tr>
<td>Bone marrow aspirate with differential to include percentages of blasts, promyelocytes, myelocytes, eosinophils and basophils.</td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td></td>
</tr>
<tr>
<td>Reverse transcriptase quantitative polymerase chain reaction (RT-q-PCR) for BCR-ABL1 mRNA transcripts.</td>
<td></td>
</tr>
</tbody>
</table>

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 Leukaemia Net (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.

If the patient is a potential transplant candidate and leukapheresis is being considered, ensure virology tests are documented, including the ones set out above and HTLV. 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

<table>
<thead>
<tr>
<th>Phase of disease</th>
<th>ELN criteria</th>
<th>WHO criteria</th>
</tr>
</thead>
</table>
| **Accelerated phase** | • Blast 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 × 10⁹/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 × 10⁹/L) unrelated to therapy  
• CCA/Ph+* on treatment  
• Thrombocytosis (>1000 × 10⁹/L) unresponsive to therapy  
• Increasing spleen size and increasing WBC count unresponsive to therapy |
| **Blast phase/crisis** | • Blast 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** (see Annex 1):

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

For contact details of SIHMDS or current diagnostic services please see Annex 4.

### 3.3. Imaging

All patients may have an ultrasound of the abdomen performed at diagnosis to document spleen (and liver) size, and thereafter when clinically appropriate.
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.

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sokal</th>
<th>Hasford</th>
<th>EUTOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.116 × (age – 43.4)</td>
<td>0.666 when &gt;50 y</td>
<td></td>
</tr>
<tr>
<td>Spleen (cm below costal margin)</td>
<td>0.0345 × (spleen size – 7.51)</td>
<td>0.042 × spleen size</td>
<td></td>
</tr>
<tr>
<td>Platelets × 10^9/L</td>
<td>0.188 × [(plts – 700)^2 – 0.563]</td>
<td>1.0956 when &gt;1,500</td>
<td></td>
</tr>
<tr>
<td>PB basophils %</td>
<td>Not included</td>
<td>0.20399 when &gt;3%</td>
<td>7 × %</td>
</tr>
<tr>
<td>PB eosinophils %</td>
<td>Not included</td>
<td>0.0413 × %</td>
<td>4 × spleen</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk classification</th>
<th>Sokal</th>
<th>Hasford</th>
<th>EUTOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>&lt;0.8</td>
<td>≤780</td>
<td>≤87</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>0.8–1.2</td>
<td>781–480</td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>&gt;1.2</td>
<td>&gt;1,480</td>
<td>&gt;87</td>
</tr>
</tbody>
</table>

Table 5: Calculation of relative risk

<table>
<thead>
<tr>
<th>Study</th>
<th>Calculation</th>
<th>Risk definition by calculation</th>
</tr>
</thead>
</table>
| Sokal et al. 1984³           | 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. 1998⁴    | 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. 2011⁵   | 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:

<table>
<thead>
<tr>
<th>Prognosis</th>
<th>Hasford score</th>
<th>Sokal score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>≤780</td>
<td>&lt;0.8</td>
</tr>
<tr>
<td>Moderate</td>
<td>&gt;780–≤1,480</td>
<td>0.8–1.2</td>
</tr>
<tr>
<td>Poor</td>
<td>&gt;1,480</td>
<td>&gt;1.2</td>
</tr>
</tbody>
</table>
Online calculators:

www.leukemia-net.org/content/leukemias/cml/cml_score/index_eng.html for Sokal and Hasford and
www.leukemia-net.org/content/leukemias/cml/eutos_score/index_eng.html for EUTOS.
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. Consideration may be given to therapeutic leukapheresis in addition to buffy coat cell collection. 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) for the first three months of therapy in order to avoid symptoms of gout and other complications.

5.3. Management of haematological adverse events (chronic phase)

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>Hold therapy if grade ≥3 until ANC ≥1.5  &lt;br&gt; Restart at lower dose if second occurrence  &lt;br&gt; Consider G-CSF if recurrent/persistent, or sepsis</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Hold therapy if platelets &lt;50 × 10⁹/L until ≥75 × 10⁹/L  &lt;br&gt; Restart at lower dose if second occurrence</td>
</tr>
<tr>
<td>Anaemia</td>
<td>Treatment interruption/dose reduction usually not indicated  &lt;br&gt; Consider erythropoietin or darbepoe tin alfa</td>
</tr>
</tbody>
</table>

5.4. Management of haematological adverse events (advanced phases)

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>Hold therapy if grade ≥4 and unrelated to disease  &lt;br&gt; Restart once ANC ≥1.0  &lt;br&gt; Restart at lower dose if second occurrence</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Hold therapy if platelets &lt;10 × 10⁹/L and unrelated to disease  &lt;br&gt; Restart once platelets ≥20 × 10⁹/L  &lt;br&gt; Restart at lower dose if second occurrence</td>
</tr>
<tr>
<td>Anaemia</td>
<td>Treatment interruption/dose reduction usually not indicated</td>
</tr>
</tbody>
</table>
5.5. Management of non-haematological adverse events

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin rash</td>
<td>Symptomatic therapy (e.g. antihistamines); topical steroids; occasionally systemic steroids (prednisolone 0.5–1mg/kg)</td>
</tr>
<tr>
<td>Elevated transaminases</td>
<td>Grade 1 or 2: monitor Grade 3: interrupt therapy, restart a lower dose when recovered with 0.5–1mg/kg prednisolone</td>
</tr>
<tr>
<td>Elevated bilirubin</td>
<td>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</td>
</tr>
<tr>
<td>Hyperglycaemia</td>
<td>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; close monitoring and adjustment of hypoglycaemic agents as needed</td>
</tr>
<tr>
<td>Muscle cramps</td>
<td>Magnesium glycerophosphate or calcium carbonate may sometimes help Electrolyte replacement if needed (e.g. potassium, calcium, magnesium) Quinine sulphate is usually ineffective</td>
</tr>
<tr>
<td>Arthralgia, bone pain</td>
<td>NSAID; the intensity of the pain declines with time</td>
</tr>
<tr>
<td>Peripheral oedema</td>
<td>Diuretics as needed (usually furosemide)</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>Take imatinib with food Anti-emetics if necessary</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Loperamide</td>
</tr>
<tr>
<td>Periorbital oedema</td>
<td>Steroid-containing cream</td>
</tr>
</tbody>
</table>
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 the Sokal/Hasford score and 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 LCA has produced a Key Worker Policy (see Appendix 4: LCA Key Worker Policy) which sets out the definition of a key worker and provides an overview of their role and responsibilities.

The clinical nurse specialist should ensure that all patients are offered a holistic needs assessment (HNA) (see Appendix 5: LCA Holistic Needs Assessment Tool) 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 Leukaemia & Lymphoma Research Fund (LLR) CML information booklet, International CML Foundation, Macmillan Cancer Support information websites and the NHS Information Prescription are good sources of patient information at diagnosis and can be downloaded from the websites below:

https://leukaemialymphomaresearch.org.uk/information/leukaemia/chronic-myeloid-leukaemia-cml
www.cml-foundation.org
www.macmillan.org.uk/Cancerinformation/Cancerinformation.aspx
www.nhs.uk/ipg/pages/ipstart.aspx

Patients should have access to supportive care information and rehabilitation throughout the cancer pathway. Consider referral to the appropriate services, including rehabilitation, when indicated. Please refer to section 11: Rehabilitation and Survivorship.
7. Treatment

See Annex 3 for TKI drug interactions.

When discussing oral treatments with patients for the first time, ensure that the oral chemotherapy patient education checklist (see Annex 2) is used and signed off.

Some centres may also have hand-held chemotherapy booklets.

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

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, 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%.

In randomised trials of nilotinib and dasatinib vs 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). 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. Once in CCyR, BCR–ABL1 transcript numbers in the blood should be regularly measured. The achievement of a major molecular response (MMR or MR³) (Table 6) has been shown to be associated with a reduced risk of loss of CCyR.

In patients who lose CCyR, a kinase domain (KD) mutation analysis should be performed and a second-generation TKI introduced without delay. Second-generation TKIs induce CCyR in approximately 50% of patients who are resistant to imatinib. Useful responses have also been identified using the third-generation agent ponatinib in patients who have failed at least two TKIs. 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. Ponatinib is available for patients with a T315I mutation from the Cancer Drugs Fund (CDF).

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.
7.1.2. First-line treatment

Hydroxycarbamide and allopurinol should be initiated if the WBC is elevated (e.g. ≥80–100 × 10⁹/L), to reduce WBC counts and to minimise complications associated with tumour lysis.

Both imatinib 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 or Hasford score, co-morbidities and patient choice. Patients with high-risk Sokal/Hasford scores, or with major route clonal chromosome abnormalities (CCA) at diagnosis should have HLA-typing if considered fit for an AlloSCT. In the absence of cardiovascular co-morbidities, nilotinib 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. Patients who are started on front-line imatinib or nilotinib should have their BCR-ABL transcript level monitored three months after the start of treatment. Those who have not achieved an early molecular response (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, although there are no clear data or guidelines regarding the best course of action.⁸ ¹⁴ ¹⁵

7.1.3. Second-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 (Table 7 and Table 8) should have HLA-typing (together with their siblings), a KD mutation analysis and be started on a second-generation TKI. 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.

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%. If blastic transformation evolves during imatinib, treatment with dasatinib combined with intensive chemotherapy (i.e. for acute myeloid leukaemia/acute lymphoblastic leukaemia) should be given. Dasatinib is the preferred TKI because of its ability to cross the blood–brain barrier.¹⁶ Consideration should also be given to the administration of intrathecal therapy. Responses to TKIs are transient in advanced phases. Therefore, if a return to CP (‘second’ CP) or a complete remission has been achieved, patients should proceed to an AlloSCT if appropriate and if a donor has been identified.¹⁷ Patients with de novo AP should be considered for AlloSCT unless they achieve an optimal response with TKIs.
Table 6: Conventional definitions of cytogenetic and molecular responses to treatment for chronic myeloid leukaemia

<table>
<thead>
<tr>
<th>Ph-positive marrow metaphases (%)</th>
<th>Designation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Complete cytogenetic response (CCyR)</td>
</tr>
<tr>
<td>1–35</td>
<td>Partial cytogenetic response (PCyR)</td>
</tr>
<tr>
<td>36–95</td>
<td>Minor cytogenetic response</td>
</tr>
<tr>
<td>&gt;95</td>
<td>None</td>
</tr>
</tbody>
</table>

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).

<table>
<thead>
<tr>
<th>Ratio of BCR-ABL to ABL (%)</th>
<th>Designation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤0.1% BCR-ABL&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Major molecular response (MMR or MR&lt;sup&gt;3&lt;/sup&gt;)</td>
</tr>
<tr>
<td>Detectable disease ≤0.01% BCR-ABL&lt;sup&gt;15&lt;/sup&gt; or undetectable disease in cDNA with ≥10,000 ABL transcripts</td>
<td>MR&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Detectable disease ≤0.0032% BCR-ABL&lt;sup&gt;15&lt;/sup&gt; or undetectable disease within cDNA with ≥32,000 ABL transcripts</td>
<td>MR&lt;sup&gt;4.5&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>Optimal</th>
<th>Warning</th>
<th>Failure</th>
</tr>
</thead>
</table>
| Baseline                 | N/A     | High risk  
or  *CCA/Ph+, major route | N/A                      |
| 3 months                 | BCR-ABL1 ≤10% and/or Ph+ ≤35% | BCR-ABL1 >10% and/or Ph+ 36–95% | Non-CHR and/or Ph+ >95% |
| 6 months                 | BCR-ABL1 <1% and/or Ph+ 0    | BCR-ABL1 1–10% and/or Ph+ 1–35% | BCR-ABL1 >10% and/or Ph+ >35% |
| 12 months                | BCR-ABL1 ≤0.1%                | BCR-ABL1 >0.1–1%                 | BCR-ABL1 >1% and/or Ph+ >0 |
| Then, and at any time    | BCR-ABL1 ≤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\textsuperscript{19}

<table>
<thead>
<tr>
<th>Timeframe</th>
<th>Optimal</th>
<th>Warning</th>
<th>Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>N/A</td>
<td>No CHR or loss of CHR on imatinib or lack of CyR to first-line TKI or high risk</td>
<td>N/A</td>
</tr>
<tr>
<td>3 months</td>
<td>$BCR$-$ABL1 \leq 10%$ and/or Ph+ &lt;65%</td>
<td>$BCR$-$ABL1 &gt;10%$ and/or Ph+ 65–95%</td>
<td>No CHR or Ph+ &gt;95% or new mutations</td>
</tr>
<tr>
<td>6 months</td>
<td>$BCR$-$ABL1 \leq 10%$ and/or Ph+ &lt;35%</td>
<td>Ph+ 35–65%</td>
<td>$BCR$-$ABL1 &gt;10%$ and/or Ph+ &gt;65% and/or new mutations</td>
</tr>
<tr>
<td>12 months</td>
<td>$BCR$-$ABL1 &lt;1%$ and/or Ph+ 0</td>
<td>$BCR$-$ABL1 1–10%$ and/or Ph+ 1–35%</td>
<td>$BCR$-$ABL1 &gt;10%$ and/or Ph+ &gt;35% and/or new mutations</td>
</tr>
<tr>
<td>Then, and at any time</td>
<td>$BCR$-$ABL1 \leq 0.1%$</td>
<td>*$CCA/Ph^-$ ($-7$, or $7q^-$) or $BCR$-$ABL1 &gt;0.1%$</td>
<td>Loss of CHR or loss of CCyR or PCyR New mutations Confirmed loss of MMR\textsuperscript{*} Mutations CCA/Ph+</td>
</tr>
</tbody>
</table>

\textsuperscript{*} In 2 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 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.

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 vs 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) (see Appendix 5: LCA Holistic Needs Assessment Tool) 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 (see Appendix 6: NCSI Treatment Summary).

- **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).

Recommendation: An end of treatment consultation should be offered to every patient when there are any significant changes in treatment and follow-up arrangements. This should include an HNA and associated written care plan, and should also include the discussion and provision of a comprehensive treatment summary.
10. Follow-up Arrangements

Patients who start on TKI should have weekly FBC, U&Es, LFTs and fortnightly clinic appointments for the first four weeks. Once FBC is within normal range, patients should attend three-monthly clinic appointments with FBC, U&Es, LFTs and BCR-ABL quantification by RQ-PCR.

A bone marrow aspirate with cytogenetics and trephine should be considered every three 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). Once CCyR is achieved, patients should be monitored by RQ-PCR (peripheral blood) for the determination of BCR-ABL transcript level.

Patients who have achieved an MMR/MR3 should be monitored every three months by peripheral blood RQ-PCR.

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. Rehabilitation and Survivorship

Patients with CML are followed lifelong on treatment within specialist haematology departments. Issues in relation to rehabilitation and the long-term consequences of treatment should be monitored throughout the patient pathway and highlighted to the appropriate allied health professionals if required. Survivorship issues can relate to the effects of the disease process and/or management of long-term adverse effects of treatment, such as TKIs, including long-term monitoring/decisions about intermittent cessation of therapy (currently in trials). Please refer to LCA Survivorship Guidelines for more information.

Any patient experiencing or reporting reduced mobility and/or ability to perform activities of daily living should be referred for occupational therapy and physiotherapy assessment.

12. Research/Clinical Trials

The LCA has produced a directory of clinical trials that are actively recruiting patients with CML. Please refer to the LCA website (www.londoncanceralliance.nhs.uk/trials) for the most up-to-date list.
13. 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. Care may be required from specialist palliative care teams which are available in all the cancer centres and units affiliated to the LCA.

To support consideration of referral to specialist palliative care, please refer to the LCA Referral Criteria for Specialist Palliative Care (see Appendix 8). The LCA form for referral to specialist palliative care can be found in Appendix 7: LCA Specialist Palliative Care Referral Form.

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.

14. 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; further details on these datasets are available in Annex 6). In line with peer review requirements, the LCA Haemato-Oncology Pathway Group and the LCA Clinical Board review this data on a regular basis to ensure all patients receive treatments intended to provide the best possible outcomes, consistent across all MDTs.
References


Annex 1: LCA Acute Leukaemias and Myeloid Neoplasms BMAT Diagnostics Summary Chart

<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>AT DIAGNOSIS</th>
<th>RESTAGING</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aspirate (NPH)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Immuno (RMH) EDTA (purple)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cytogenetics (KGC) pot (pink) – in fridge</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Molecular (KGC &amp; as indicated) EDTA (purple)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trephine (NPH) Histopath pot</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trial sample EDTA (purple) or heparin (green)</td>
<td>See last MDT discussion</td>
</tr>
</tbody>
</table>

| AML/AUL/MPL                 | YES | YES | YES | YES | YES | YES | YES | A/I/C/M/T/?TS |
| APML                       | YES | YES (PML-RARA) | YES | YES (GST) | YES | YES | YES |
| Ph+ AML or ALL             | YES | YES | YES | YES (ICHNT) | YES | YES | YES |
| ALL/Burkitt lymphoma       | YES | YES | YES | YES | YES | YES | YES |
| MDS (If ?AML/blasts on film, follow AML guide) | YES | NO | YES | YES | YES | YES | ? | A/C/M |
| MPN                        | YES | NO | NO | YES | YES | YES | YES | ? | A & C; M if +ve at diagnosis |
| CML (If ?AML/blasts on film, follow AML guide) | YES | YES | YES | YES (ICHNT FOR BCR-ABL) | YES | YES | YES | A/C/M |
| Cytopenias/Macrocytosis    | YES | ONLY IF AML/LYMPHOMA SUSPECTED | YES | NO | YES | YES | YES | ? | As indicated by diagnosis |

KGC = Kennedy Galton Regional Centre for Cytogenetics (located at NPH site, St. Mark’s Level 8; ext3104)
GST = Guy’s & St Thomas’ Hospital (call when send; 020 7188 7188, ext 51060)
ICHNT = Imperial College Healthcare NHS Trust (020 8383 2179 / 2167 / 2177) TDL = The Doctors Laboratory (Pathology Laboratory at NWLHT)
RMH = Royal Marsden Hospital (020 8722 4221)

A = Aspirate  I = Immunophenotyping  C = Cytogenetics  M = Molecular  T = Trephine  TS = Trial Sample  ? = Ask Trial Coordinators
**Annex 2: LCA Oral Chemotherapy Patient Education Checklist**

<table>
<thead>
<tr>
<th>Oral anti-cancer patient and carer education checklist</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prior to first cycle:</strong></td>
</tr>
<tr>
<td><em>This checklist must be completed with the patient/carer at the point of handing the medication to the patient, either in conjunction with or following a pre-treatment consultation.</em></td>
</tr>
<tr>
<td><strong>Tick if discussed with the patient/carer</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Instructions for taking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Explain how and when to take the medicine, including any treatment breaks.</td>
</tr>
<tr>
<td>If the patient is unable to swallow tablets or capsules or has a feeding tube, please refer to the oral systemic anti-cancer therapies (SACT) counselling handbook to dissolve or open capsules (if appropriate for the oral anti-cancer medicine).</td>
</tr>
<tr>
<td>Missed doses can be taken if near to the scheduled time. Otherwise, do not try and catch up or double the next dose. Wait until the next dose is due.</td>
</tr>
<tr>
<td>In case of vomiting after taking a dose, do not repeat the dose. Take the next dose at the normal time. If this occurs again, contact the chemotherapy team/24-hour advice line.</td>
</tr>
<tr>
<td>Check that the patient is aware of side effects and has received written information. Any side effects should be reported to your chemotherapy nurse or doctor.</td>
</tr>
<tr>
<td>If the patient is taking any prescribed/over-the-counter medicine/supplement – the patient should inform their medical team.</td>
</tr>
<tr>
<td>Return any unused oral anti-cancer medicine to the hospital pharmacy. Do not flush or throw them away (for high-cost drugs see the counselling handbook).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Storage and handling</th>
</tr>
</thead>
<tbody>
<tr>
<td>The oral anti-cancer medicine should not be handled by anyone who is pregnant or planning a pregnancy (except on the advice of medical team).</td>
</tr>
<tr>
<td>If the carer is giving the anti-cancer medicine, they should not handle the medicine directly but wear gloves or push the medicine out of the blister pack (if applicable) directly into a medicine pot.</td>
</tr>
<tr>
<td>Store the tablets/capsules in the container provided.</td>
</tr>
<tr>
<td>Store the tablets/capsules in a secure place, away from and out of sight of children.</td>
</tr>
<tr>
<td>Wash hands thoroughly after taking/giving the oral anti-cancer medicine.</td>
</tr>
</tbody>
</table>
Check that the patient understands how to take the treatment, by asking them to repeat back their instructions.

**Written information provided**

- ‘Taking an oral anti-cancer medicine’ patient information sheet
- Diary for taking your oral anti-cancer medicine (if applicable)
- For swallowing difficulty only – give relevant factsheet if appropriate for the oral anti-cancer medicine and an oral anti-cancer pack with disposables (e.g. oral/enteral syringes)
- Dissolving oral anti-cancer tablets safely
- Opening oral anti-cancer capsules safely
- Giving an oral anti-cancer medicine through a feeding tube
- Giving an anti-cancer syringe by mouth

<table>
<thead>
<tr>
<th>Patient name</th>
<th>Counselling/educated by</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital number</td>
<td>Pharmacist/Pharmacy technician/Nurse/Interpreter</td>
</tr>
<tr>
<td>Signature and date</td>
<td>Signature and date</td>
</tr>
</tbody>
</table>

**Before all subsequent cycles:**

Check that the patient has understood the checklist above and repeat if necessary.

Check that any side effects experienced with their previous cycle were discussed with their medical team.

If a dose adjustment has been made, check that the patient is aware why their dose has been changed and how many tablets/capsules they should now take.

Check that the patient had no problems taking their previous cycle.

Check that the patient understands how to take the treatment, by asking them to repeat back their instructions.

Please retain a copy and/or endorse the prescription/electronic patient record as evidence counselling took place at each cycle.
Annex 3: 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.

- \textit{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 P-gp (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.
Annex 4: SIHMDS or Current Diagnostic Services and Contacts

Guy’s & St Thomas’ NHS Foundation Trust
Cytogenetics/Flow Lab
ViaPath Pathology
4th Floor, Southwark Wing
Guy’s Hospital
Great Maze Street
London SE1 9RT

Imperial College Healthcare NHS Trust
Imperial Molecular Pathology Laboratory
G Block, North Corridor
Hammersmith Hospital
Du Cane Road
London W12 0HS

London North West Healthcare NHS Trust
Processed centrally in TDL laboratories on-site for SIHMDS (in progress), cytogenetics/molecular to:
North West Thames Regional Genetics Service, Haematology Section
Northwick Park Hospital
Watford Road
Harrow HA1 3UJ

The Royal Marsden Hospital NHS Foundation Trust
The Centre for Molecular Pathology
Downs Road
Sutton SM2 5PT
Tel: 020 8915 6570
Immunophenotyping Tel: 020 8915 6517 or 020 8915 6518
Cytogenetics Tel: 020 8722 4232
Molecular Genetics Tel: 020 8915 6565

For APML diagnostic and MRD
Dr Yvonne Morgan
Molecular Oncology Diagnostics Unit
GSTT Pathology, 4th Floor, Southwark Wing
Guy’s Hospital
Great Maze Street
London SE1 9RT

King’s College Hospital NHS Foundation Trust
KingsPath: Clinical Diagnostic Pathology Service
Haematological Medicine
King’s College Hospital
Denmark Hill
London SE5 9RS
Annex 5: JACIE-accredited Transplant Centres in the LCA

**Imperial College Healthcare NHS Trust**
Dr Eduardo Olavarria  
Consultant Haematologist  
BMT Programme Director  
Haematology Department  
ICHNT  
Hammersmith Hospital  
Du Cane Road  
London, W12 0HS  
Tel: 020 8383 3237  
Fax: 020 8742 9335  
Email: eduardo.olavarria@imperial.nhs.uk

**The Royal Marsden NHS Foundation Trust**
The Royal Marsden NHS Foundation Trust  
Dr Mike Potter via 020 8661 3670  
katrina.sharpe@rmh.nhs.uk  
Dr Chloe Anthias, contact details as above.  
Dr Mark Ethell, via 020 8661 3794,  
PA: janet.bromell@rmh.nhs.uk

**Department of Haemato-Oncology**
**The Royal Marsden NHS Foundation Trust**
RS11, 2nd Floor, Orchard House,  
Downs Road, Sutton,  
Surrey, SM2 5PT  
Tel: 020 8661 3670  
Fax: 020 8642 9634 (safe haven)  
Alternative email: katrina.sharpe@nhs.net

**St George’s University Hospitals NHS Foundation Trust**
Dr Mickey Koh  
Director: Stem Cell Transplantation  
Consultant Haematologist  
St George’s Hospital and Medical School  
Jenner Wing Corridor 6  
Blackshaw Road  
London, SW17 0QT  
Tel: 020 8725 3545  
Fax: 020 8725 2859  
Email: mickey.koh@stgeorges.nhs.uk

**King’s College Hospital NHS Foundation Trust**
Bone Marrow Transplant Team  
4th Floor, Hambleden Wing  
King’s College Hospital  
Denmark Hill  
London, SE5 9RS  
Tel: 020 3299 4694, 020 3299 5268
Annex 6: Data Requirements

Haematology oncology services within the LCA are required to submit data to the following nationally mandated datasets for all patients diagnosed with haematological cancers.

The Cancer Outcomes and Services Dataset (COSD)

The core dataset for all tumour types including haematological cancers is mandated from January 2013, and the site-specific dataset is mandated from July 2013. Details of the dataset can be found on the National Cancer Intelligence Network website:


The local cancer registry will be collating this dataset using Trust data feeds which should include all these items. The feeds are:

- Trust PAS
- Trust pathology
- Trust radiology
- Trust multidisciplinary team (MDT) feed.

In line with the requirements set out in Provider Trust contracts, this data should be submitted within 25 workings days of the end of the month in which the activity took place.

<table>
<thead>
<tr>
<th>Three groups of haematological cancers are considered stageable by the Registry:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphomas, using Ann Arbor (or Murphy St Jude for children)</td>
</tr>
<tr>
<td>Myelomas, using ISS</td>
</tr>
<tr>
<td>CLLs, using Rai and Binet</td>
</tr>
</tbody>
</table>

For the purposes of COSD, any other haematological cancers are not counted as stageable.

| For CLL both Rai (0-IV) and Binet (A-C) stages need to be recorded and submitted to COSD to be considered “fully staged” |

MGUS does not need to be recorded and submitted as it is not defined as an invasive tumour.

Systemic Anti-Cancer Therapy dataset (SACT)

Provider Trusts that provide chemotherapy to patients are required to submit data to the SACT dataset. Details of the audit and the dataset requirements are available on the dataset homepage:

www.chemodataset.nhs.uk/home.aspx
Radiotherapy Dataset (RTDS)

Provider Trusts that provide radiotherapy to patients are required to submit data to the RTDS dataset. Details of the audit and the dataset requirements are available on the dataset homepage: http://www.canceruk.net/rtservices/rtds/

Cancer Waiting Times dataset

Trusts are required to submit data to the Cancer Waiting Times dataset, which includes details of all patients who are referred as a 2 week wait (2ww) referral, and all patients who are treated for cancer. Trusts are required to submit this data within 25 working days of the month of either when the patient was first seen for the 2ww target, or when the patient was treated. The cancer waiting times dataset can be found at: www.datadictionary.nhs.uk/data_dictionary/messages/clinical_data_sets/data_sets/national_cancer_waiting_times_monitoring_data_set_fr.asp

Local data requirements

The LCA Haematology Oncology Pathway group is working on developing a suite of metrics to inform the group and services within the LCA on areas of priority and potential service improvement. The LCA is currently collating information which is available through sources of data currently available, though the Haematology Oncology Pathway Group or LCA clinical board may require Trusts to submit additional MDT data to the LCA if additional priority areas are identified.
### Annex 7: Multidisciplinary Teams (MDTs) and Constituent Hospital Trusts

<table>
<thead>
<tr>
<th>South East London MDT 1</th>
<th>Guy’s &amp; St Thomas’ NHS Foundation Trust/Lewisham and Greenwich NHS Trust (Lewisham Hospital and Queen Elizabeth Hospital)</th>
</tr>
</thead>
<tbody>
<tr>
<td>South East London MDT 2</td>
<td>King’s College Hospital NHS Foundation Trust (including Princess Royal University Hospital)</td>
</tr>
<tr>
<td>South West London MDT 1</td>
<td>Kingston Hospital NHS Foundation Trust/St George’s University Hospitals NHS Foundation Trust</td>
</tr>
<tr>
<td>South West London MDT 2</td>
<td>Epsom and St Helier University Hospitals NHS Trust/Croydon Health Services NHS Trust</td>
</tr>
<tr>
<td>South West London MDT 3</td>
<td>The Royal Marsden NHS Foundation Trust</td>
</tr>
<tr>
<td>North West London MDT 1</td>
<td>Imperial College Healthcare NHS Trust/The Hillingdon Hospitals NHS Foundation Trust/Chelsea and Westminster Hospital NHS Foundation Trust/West Middlesex University Hospital NHS Trust/Ealing Hospital</td>
</tr>
<tr>
<td>North West London MDT 2</td>
<td>The London North West Healthcare NHS Trust (Northwick Park Hospital and Central Middlesex Hospital)</td>
</tr>
</tbody>
</table>
Appendices

Appendix 1: 2 Week Wait Referral Forms
- North West London
- South East London
- South West London

Appendix 2: Treatment of Children

Appendix 3: Treatment of Teenagers and Young Adults
- Teenagers and Young Adults PTC Referrals
- Teenagers and Young Adults MDT Proforma

Appendix 4: LCA Key Worker Policy

Appendix 5: LCA Holistic Needs Assessment Tool

Appendix 6: NCSI Treatment Summary

Appendix 7: LCA Specialist Palliative Care Referral Form

Appendix 8: LCA Referral Criteria to Specialist Palliative Care