

The Management of Leukaemia

Oncological Treatment Guidelines for the Management of Leukaemia & Pathway of Care

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Table of Contents

1.0	GENERAL HAEMATOLOGY OVERVIEW	4
2.0	SCOPE	4
3.0	PROCESS AND TERMINOLOGY	5
3.1	TUMOURS	5
3.2	REFERRAL GUIDELINES AND PROCESS	5
3.3	GP ALERT (NICE: REFERRAL GUIDELINES FOR SUSPECTED CANCER – JUNE 2005)	5
4.0	IMAGING	6
5.0	PATHOLOGY	6
6.0	SPECIALIST PALLIATIVE CARE AND SUPPORT	6
7.0	CLINICAL TRIALS	6
8.0	FOLLOW UP	7
9.0	DATA	7
10.0	PERSONNEL AND CONTACT INFORMATION	8
11.0	MANAGEMENT OF LEUKAEMIA	9
11.1	TREATMENT ALGORITHM	9
11.2	DIAGNOSTIC CRITERIA	10
11.2.1	<i>Core Criteria</i>	10
11.2.2	<i>Essential Investigations</i>	10
11.3	TREATMENT	11
11.3.1	<i>Definitions</i>	11
11.3.2	<i>Primary Treatment</i>	11
11.3.3	<i>Poor risk, refractory or relapsed patients (Kantarjian, Gandhi et al. 2003; Craddock, Tauro et al.2005)</i>	12
11.4	ACUTE LYMPHOBLASTIC LEUKAEMIA	12
11.4.1	<i>Precursor B-cell Lymphoblastic Leukaemia</i>	12
11.4.2	<i>Precursor T-lymphoblastic Leukaemia</i>	12
11.4.3	<i>Essential Investigations</i>	13
11.4.4	<i>Primary Treatment (Manera, Ramirez et al. 2000; Vilmer, Suciú et al. 2000; Annino, Vegna et al. 2002; Pui, Cheng et al. 2003)</i>	13
11.4.5	<i>Treatment of primary refractory disease</i>	14
11.4.6	<i>Treatment of ALL relapsing after CR (Fielding, Richards et al. 2007)</i>	14
11.4.7	<i>CNS leukaemia at diagnosis</i>	15
11.4.8	<i>Special issues in antimicrobial prophylaxis</i>	15
11.5	HAIRY CELL LEUKAEMIA	15
11.5.1	<i>Presentation</i>	15
11.5.2	<i>Investigations</i>	16
11.5.3	<i>Treatment of HCL</i>	16
11.5.4	<i>Splenectomy</i>	17
11.6	REFERENCES FOR HCL	17
11.7	MANAGEMENT PLAN FOR CLL/LYMPHOCYTIC NHL	18
11.7.1	<i>Diagnostic Criteria</i>	18
11.7.2	<i>Prognostic factors (BSCH guidelines, BJH 2004)</i>	18
11.7.3	<i>Investigations</i>	19
11.8	MANAGEMENT OF CLL	19
11.8.1	<i>Monoclonal B-lymphocytosis (CLL phenotype) – MBL-CLL</i>	19

11.8.2	<i>Early stage (Binet's stage A) CLL</i>	20
11.8.3	<i>Advanced stage CLL requiring therapy</i>	20
11.8.4	<i>Initial therapy for advanced CLL</i>	20
11.8.5	<i>Relapsed but not refractory CLL (fludarabine-sensitive relapse)</i>	21
11.8.6	<i>Fludarabine-refractory CLL</i>	22
11.8.7	<i>Fludarabine and Alemtuzumab refractory CLL</i>	22
11.8.8	<i>Allogeneic stem cell transplantation</i>	22
11.8.9	<i>Richter's Transformation</i>	22
11.9	CML	23
11.9.1	<i>Investigations at Diagnosis</i>	23
11.9.2	<i>WHO criteria for the definition of phases of CML¹</i>	23
11.9.3	<i>Allografting for chronic myeloid leukaemia</i>	24
11.9.4	<i>First line therapy with imatinib or nilotinib: see flow charts</i>	24
11.9.5	<i>Suggestions for the use of 2nd generation tyrosine kinase inhibitors (TKIs) (Dasatinib, nilotinib) in patients with chronic phase chronic myeloid leukaemia</i>	27
11.9.6	<i>Refractory Chronic phase, accelerated phase, or blast crisis CML or significant intolerance to dasatinib/nilotinib</i>	28
11.9.7	<i>Treatment of CML with T315I mutation</i>	28
11.9.8	<i>References for CML</i>	28
12.0	ACKNOWLEDGEMENTS	30
13.0	GLOSSARY	30
14.0	DOCUMENT ADMINISTRATION	31

1.0 General Haematology Overview

- This document has been written to provide guidance on the treatment of leukaemia in Kent & Medway. These guidelines describe the process for ensuring that all leukaemia cases diagnosed within the Kent & Medway region are managed by the designated Haematological Cancer MDTs, achieving a coordinated seamless patient pathway in accordance with the best possible evidence based practice and to facilitate advancement in the specialty in the field of haematological cancer management.
- Please see the chemotherapy prescribing proformas / Network Chemotherapy Prescribing Manual for details on chemotherapy / anti-cancer regimens.
- All patients will be considered for entry into a clinical trial (see appendix A).
- All patients should be discussed within a multidisciplinary team meeting before commencing treatment.
- All 16-24 year olds must be notified to the TYA MDT. All young people aged 16-18 must be referred to the TYA Principle Treatment Centre (PTC) which for Kent & Medway is based at the Royal Marsden Hospital. Referral to a TYA PTC does not necessarily mean that treatment will be undertaken at that centre; shared care management protocols may allow some treatments to be delivered locally. Young people aged 19-24 have the option of being referred to the Royal Marsden Hospital for treatment but may choose to be treated locally however they should have their treatment discussed with the TYA PTC.

Notes:

- The Kent & Medway - Cancer, Haematology Tumour Site Specific Group (TSSG) is responsible for agreeing all of the guidance
- The TSSG should consult with primary care members of the Kent & Medway Clinical Commissioning Groups (CCGs) regards the development of the pathway
- The purpose of the document is to provide a framework for the management of patients with suspected/confirmed prostate cancer
- The overall management details are largely reflected in the updated flow charts
- Information on MDT “functioning” is confined to the MDT Operational Policies based on the TSSG agreed “High Level Operational Policy” which is located on the [Kent & Medway – Cancer website: http://www.kmcn.nhs.uk/home/resource-library](http://www.kmcn.nhs.uk/home/resource-library)

2.0 Scope

This Standard Operating Procedure (SOP) applies to all cases and suspected cases of Haematological Cancer within Kent & Medway and haematological cancer specification of delivery of care requires all Trusts within Kent & Medway to adopt an agreed policy for the delivery of care. The policy relates to the expected pathway of care / treatment regimes for patients diagnosed with haematological cancer.

The policy covers the following:

- Access
- Initial Assessment
- Investigations
- Colorectal cancer multidisciplinary meeting (MDM)
- Surgical and non-surgical treatment
- Recurrent disease
- Follow up

3.0 Process and Terminology

3.1 Tumours

- B-Cell lymphoproliferative disorders including myeloma
- Chronic myeloproliferative disorders
- Acute lymphoblastic leukaemia
- Acute myeloid leukaemia
- Myelodysplastic syndromes
- Chronic myeloid leukaemia

3.2 Referral guidelines and process

- The incidental finding of haematological malignancy on specimens sent for routine examination is common. In these circumstances the haemato-oncologist will often be the clinician advising the GP that the patient requires an urgent appointment. Delays should NOT be built into the system by insisting on the use of a rapid access proforma.
- In the unlikely event that a GP receives a blood count/film reported as acute leukaemia (Or any of the conditions outlined above) and not directly contacted by a haematologist – the patient should be referred to a specialist immediately.
- Patients with spinal cord compression or renal failure suspected of being caused by myeloma require immediate referral to a haematologist.
- Patients with unexplained splenomegaly should be referred urgently to a haematologist.
- Patients referred to head & neck lump clinics who are found to have a haematological malignancy should be fast tracked to a haematologist. (The Head & Neck Pathway of Care reflects this)
- Patients with a “lump” referred to a surgeon and subsequently diagnosed with a haematological malignancy should be fast tracked to a haematologist.

3.3 GP alert (NICE: Referral guidelines for suspected cancer – June 2005)

- Combinations of the following signs and symptoms should alert GPs to perform a full examination, further investigations (including FBC and film) and possible referral:
 - Abdominal pain
 - Alcohol induced pain
 - Bleeding
 - Breathlessness
 - Bruising
 - Drenching night sweats
 - Fatigue
 - Fever
 - Lymphadenopathy
 - Recurrent infections
 - Splenomegaly
 - Weight loss
- GP investigations in patients with:
 - Persistent unexplained fatigue:
Carry out an FBC, ESR & C-reactive protein. Repeat at least once if the patients condition remains unexplained and does not improve.
 - Unexplained lymphadenopathy:
Carry out an FBC, ESR, & C-reactive protein.
- Any of the following additional features of lymphadenopathy:
 - Persistence for 6 weeks or more
 - Lymph nodes increasing in size
 - Lymph nodes greater than 2 cm in size
 - Widespread nature
 - Associated splenomegaly, night sweats or weight loss:
Investigate further and/or refer.
 - Unexplained bruising, bleeding and purpura or symptoms suggesting anaemia:
Carry out FBC, Film, Clotting screen, ESR, C-reactive protein.
 - Persistent and unexplained bone pain:
Carry out FBC, X-ray, U&Es, LFTs, Bone profile, PSA (in males), ESR, C-reactive protein.

4.0 Imaging

Imaging guidelines for haematological cancer can be located on the Kent & Medway – Cancer website on the following link: <http://www.kmcn.nhs.uk/home/resource-library/diagnostics-ccag/>

5.0 Pathology

All Kent & Medway reporting pathologists follow The Royal College of Pathologists Histopathology Reporting on Cancers guidelines – a copy of which is available through the Kent & Medway – Cancer website:- <http://www.kmcn.nhs.uk/home/resource-library/pathology-ccag/>

<http://www.rcpath.org/publications-media/publications/datasets/datasets-TP>

6.0 Specialist Palliative Care and Support

All patients with a Haematological Cancer will have access to specialist palliative care and support at every stage of the patient journey.

Open and frank discussions with patients should take place with patients at all stages of their journey so that patients are not confused about their prognosis or have unrealistic expectations of any of the forms of treatment offered to them.

Relatives and carers will need to be appropriately supported and given appropriate information. However, in accord with the recommendations set out in various revised Improving Outcomes Guidance, relatives and carers should not be given information different to that given to the patient.

Frail and terminally ill patients with a Haematological Cancer should always be discussed with the specialist palliative care team.

Patients with end stage disease may choose to end their days at home and therefore the options should always be discussed openly with them and their relatives/carers.

Effective communication with primary care is essential.

All patients should have unlimited access to a Haematology Cancer nurse specialist who is a member of the specialist Haematology Cancer team.

7.0 Clinical Trials

Suitability for entry into Kent & Medway - Cancer agreed clinical trials should be a standard component of the MDM discussion on each patient with a Haematological Cancer.

Refer to the local research team who will provide on request an orientation handbook, list of current trials and associated trial protocols and summaries.

Contact numbers

MTW – Clinical Trials Office	01622 225033
Darent Valley Hospital – Clinical Trials Office	01322 428100 ext 4810
Medway Maritime Hospital – Clinical Trials Office	01634 825094
East Kent Hospitals – Clinical Trials Office	01227 864129

Dr J Lindsay	Consultant Haematologist/ MDT Lead	01227 864072
Dr C Pocock	Consultant Haematologist	01227 864071
Dr K Saied	Consultant Haematologist	01843 225544 ext 62407
Dr V Ratnayake	Consultant Haematologist	01233 651822
Malignant/ ward attending SpR	Specialist Registrar	01227 766877 Bleep 7163
Jane Baxter	Clinical Nurse Specialist	01227 766877 Bleep 7065
Lavinia Parsons	Clinical Trials Unit	01227 864129
Anna Lamb	MDT Coordinator	01227 766877 ext 74463
Julia Davis	Haematology Office Manager/Medical Secretary	01227 864071

8.0 Follow Up

To be reviewed by Haematology TSSG during the period 2013/14.

9.0 Data

Collection of data at each stage of the pathway is the responsibility of the team looking after the patient at that time. The minimum dataset agreed by the TSSG will be a combination of those data items that meet national requirements, and additional items as agreed by the TSSG.

National data requirements will include:

- Cancer Waiting Times monitoring, including Going Further on Cancer Waits. The data items required will be as defined in ISB0147 at the time of referral and/or treatment.

Details of the Cancer Waiting Times dataset are available from:

<http://www.connectingforhealth.nhs.uk/nhais/cancerwaiting/documentation>

Cancer Waiting Times data will be submitted according to the timetable set out in the National Contract for Acute Services.

- The Cancer Outcomes and Services Dataset. The data items will be as defined in ISB1521, and any subsequent versions, at the time of diagnosis and/or treatment. The requirement will include those fields listed in the “Core” section of the dataset, and any additional tumour site specific sections, as applicable.

Details of the COSD are available from:

http://www.ncin.org.uk/collecting_and_using_data/data_collection/cosd.aspx

Cancer Registration and Cancer Outcomes and Services (COSD) data will be submitted according to the timetable set out by Thames Cancer Registry.

- Where applicable, teams will also collect additional data items as defined in any corresponding National Clinical Audit Support Programme (NCASP) audit dataset.

Details of these datasets are available from:

<http://www.ic.nhs.uk/services/national-clinical-audit-support-programme-ncasp/cancer>

Data for NCASP audits will be submitted, where applicable, according to timetables as agreed by the TSSG, and within the overall submission deadlines for each audit.

Submission of data to meet these national requirements will be the responsibility of each individual Trust.

Note that these standards are subject to variation from time to time, and where these requirements change, the data items required to be collected by the team will also change in line with national requirements.

Local data requirements will include any additional data items as agreed by the TSSG. These must be selected to avoid overlap with any existing data items, and where possible must use standard coding as defined in the NHS Data Dictionary.

Where possible and applicable, InfoFlex will be used for the collection and storage of data.

Additional areas of the COSD, relating to pathology, radiotherapy, SACT, diagnostic imaging and basic procedure details will feed into the dataset from other nationally mandated sources. It is the responsibility of each team to ensure that the whole of the relevant dataset is collected, and it is acknowledged that this may come from a variety of sources.

10.0 Personnel and Contact Information

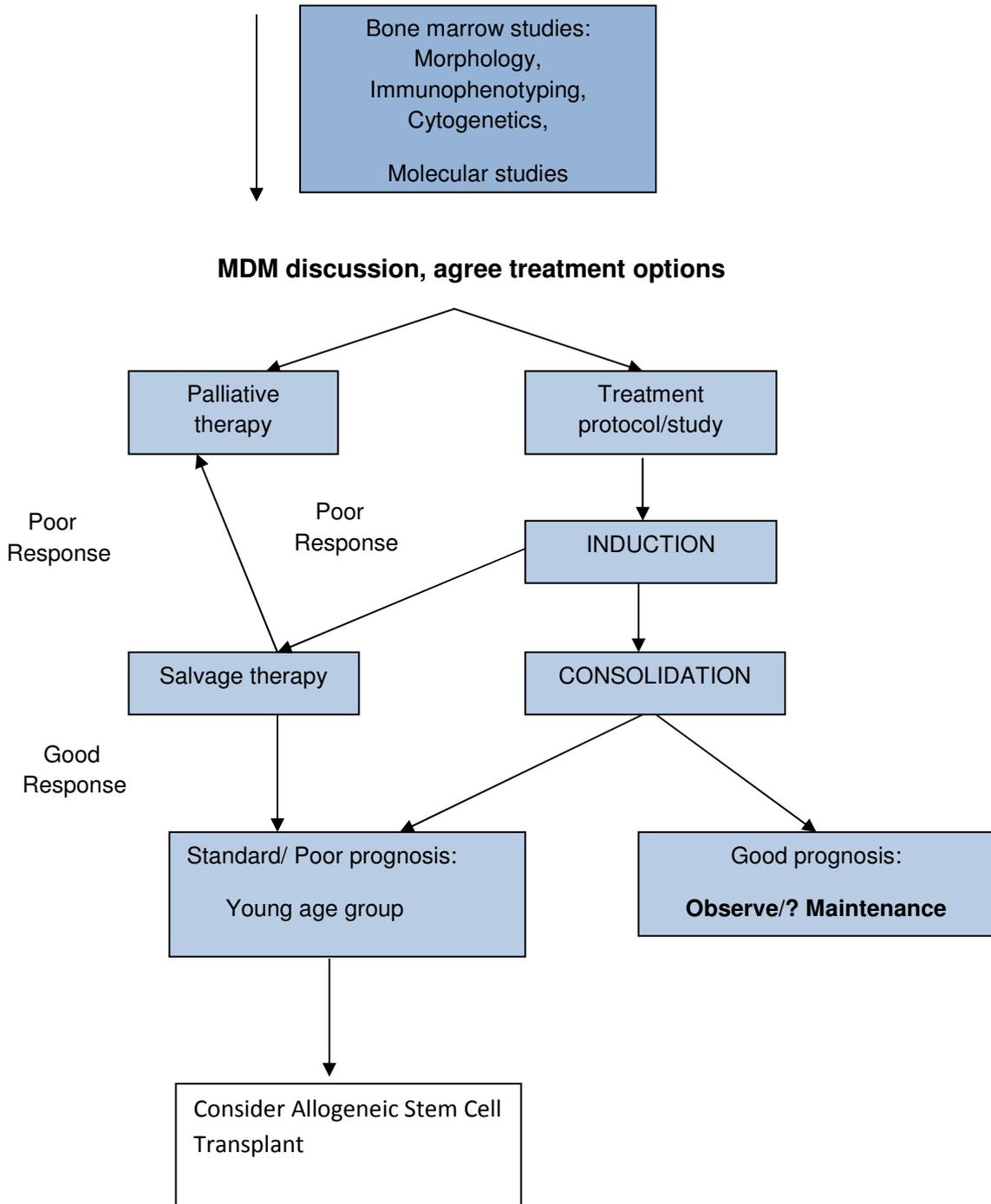
A comprehensive, up to date list of MDM contact details can be found on the Kent & Medway – Cancer website via the following link: <http://www.kmcn.nhs.uk/home/resource-library/pathology-ccag/>

11.0 Management of Leukaemia

11.1 Treatment algorithm

ACUTE MYELOID LEUKAEMIA

Diagnosis: Blood picture/clinical findings



11.2 Diagnostic Criteria

11.2.1 Core Criteria

- More than 20% myeloid blast cells by flow cytometry, or morphology including bone marrow trephine biopsy with immunohistochemistry.
- Peripheral blood (PB) with high white count in older patients is acceptable.
- Myeloid lineage demonstrated by immunophenotype
- The immunophenotype can be one of two patterns:
 - Type A: CD34+, CD117+, CD13+, CD33+, HLA-DR+, cCD3-, cCD79-
 - Type B: CD34-, CD117+, CD13+, CD33+, CD15var+, cCD3-, cCD79-, MPO+ (by flow)
- Intermediate phenotypes occur and are acceptable to define myeloid lineage
- Cytogenetics allows risk stratification. Conventional karyotyping is restricted to the initial/diagnostic evaluation of patients aged 70 or less, and should be supplemented by PCR for the balanced translocations and the *Flt3* ITD
- Molecular analysis
 - FLT3 ITD / ?TKD (not yet defined as adverse risk) 40% CN (cytogenetically normal) AML
 - MLL PTD 8% CN AML
 - NPM mutn. ~50% CN AML
 - CEBPa mutn. 15-20% CN AML
- All cases of **acute promyelocytic leukaemia (APML)** must have:
 - CD34+/-, CD13-hetero+, CD33-homo+++, CD117+, CD15-, HLA-DR-, MPO+++ (by flow)
 - Microparticulate pattern with anti-PML
 - Confirmation of t(15;17) by PCR or cytogenetics

11.2.2 Essential Investigations

- Coagulation screen
- Renal and liver function tests
- CXR
- ECG +/- echocardiogram

11.3 Treatment

11.3.1 Definitions

Induction chemotherapy is given to induce a complete remission – in NCRI (MRC) trials this is defined as a normocellular marrow with less than 5% blasts.

Consolidation or post-remission chemotherapy is necessary to prevent early relapse and increase the chance of cure, and may include stem cell transplantation.

Risk stratification is used to determine consolidation therapy. From the results of AML 10 and 11 the MRC have defined the following risk groups:

- Good risk: Any patient with favourable genetic abnormalities – t(8;21), inv(16), t(16;16), APL (see section 4.2.2)
- Standard: Any patient not in either good or poor risk groups.
- Poor risk: Any patient with more than 15% blasts in the bone marrow after Course 1, or with adverse genetic abnormalities: -5, -7, del(5q), abnormal (3q) or complex (5 or more abnormalities) – and without favourable genetic abnormalities or with *Ft3* ITD (Wheatley, Burnett et al. 1999; Grimwade, Walker et al. 2001; Kottaridis, Gale et al.2001)

11.3.2 Primary Treatment

BCSH guidelines should be followed for all AML and APL patients. (Milligan, Grimwade et al. 2006)

11.3.2.1 All cases of acute myeloid leukaemia, except acute promyelocytic leukaemia

- **Non-trial patients fit for intensive chemotherapy** should receive standard DA or ADE induction chemotherapy.
 - For patients with a complete response give consolidation chemotherapy with MACE & MidAC, HD AraC and/or stem cell transplantation. (High dose Ara-C is preferred for non-trial patients with core binding factor leukaemia and stem cell transplantation in CR1 as course 4 or 5 for non trial patients with adverse risk).
 - Patients unfit for transplant or with no suitable donor may be considered for further consolidation chemotherapy or experimental therapy.
 - For refractory patients/ no response to induction, consider high dose cytarabine or other relapse regimen (FLAG) with or without Ida or refer to tertiary centre for consideration of SCT.
 - Clofarabine may be considered in patients with relapsed / refractory disease in whom the intent is to use treatment as a bridge to bone marrow transplantation (funding approval required).
 - For relapsed patients consider high dose cytarabine or where complete response >12 months, repeat first remission inducing treatment, and where appropriate refer to tertiary centre for consideration of SCT.
- **All non-trial patients over the age of 60** with one of the forms of acute myeloid leukaemia (except Acute Promyelocytic Leukaemia), this can be any type of de novo or secondary AML – or high risk Myelodysplastic Syndrome, defined as greater than 10% marrow blasts (RAEB-2) who are fit for intensive treatment should be treated with DA.
 - Patients with a complete response and are suitably fit may be discussed with the tertiary care centre and considered for RIC allogeneic transplant.
 - For patients with relapsed disease, treatment is likely to be palliative with low dose cytarabine or hydroxycarbamide. If a prolonged first remission was achieved and the patient is fit, re-induction with DA followed by discussion with the tertiary care centre to be considered for RIC allogeneic transplant.
- Non-trial patients lacking an adverse risk karyotype are candidates for low-dose Ara-C.
- Patients not able to tolerate induction chemotherapy should be treated palliatively (this may include low dose cytarabine or hydroxycarbamide) or offered experimental therapy where available.

11.3.2.2 Acute promyelocytic leukaemia (APL)

- Non-trial patients should be treated as per AML15 Spanish arm protocol with molecular monitoring
- APL patients in complete remission (CR) should have molecular monitoring every 3 months for 2-3 years to look for signs of early relapse.

11.3.3 Poor risk, refractory or relapsed patients (Kantarjian, Gandhi et al. 2003; Craddock, Tauro et al.2005)

FLAG±Ida is an option, or similar regimen. Clinical trial is the preferred option.

All suitable patients should be discussed with the transplant centre to consider stem cell transplantation.

11.3.3.1 Relapsed APL

Follow AML15 algorithm namely arsenic trioxide (ATO) followed by stem cell transplantation (auto if PCR negative, allo if positive). Discuss with transplant centre

Older patients, if fit for induction chemotherapy and CR duration > 1 year, offer re-induction, if not fit for re-induction or short CR, experimental therapy or supportive care.

11.4 Acute Lymphoblastic Leukaemia

11.4.1 Precursor B-cell Lymphoblastic Leukaemia

Typical Cases

- Bone marrow or solid tissue infiltration with lymphoid blast cells
- Immunophenotype: CD19+, CD22+, Tdt+, CD117-, CD34var, CD45 wk

Variants

- CD10 and cytoplasmic μ heavy chain define common and pre-B subtypes according to traditional criteria. These distinctions are of no clinical value.
- *BCR-ABL* associated phenotype: CD34-homo+++, CD10-homo+, CD13+ and/or CD33+, CD38wk/-.
- t(12;21) associated: common ALL phenotype with CD10-hetero+, CD13+ and/or CD33+.

11.4.2 Precursor T-lymphoblastic Leukaemia

Typical Cases

- Bone marrow or solid tissue infiltration with lymphoid blast cells
- Immunophenotype: CD19-, Tdt+, cCD3+, CD2+, CD7+, CD22-, MPO- (by flow)
- Cytogenetic and molecular testing (including BCR-ABL)

Definition of Remission Status

When a blast cell population with a leukaemia-associated phenotype is detected unequivocally by flow cytometry on the basis of patterns of CD34, CD19, CD20 and CD10 expression or PCR this will be reported as not in remission, with the extent of infiltration stated. Where these techniques are not available remission will be defined as a morphological blast cell count of <5%.

11.4.3 Essential Investigations

- Coagulation screen
- Renal and liver function tests
- CXR
- ECG +/- echocardiogram
- Consideration of options for transplantation
- Lumbar puncture as part of treatment protocol

11.4.4 Primary Treatment (Manera, Ramirez et al. 2000; Vilmer, Suciú et al. 2000; Annino, Vegna et al. 2002; Pui, Cheng et al. 2003)

Patients aged 25 years or over with Philadelphia negative ALL:

UKALL14 trial protocol. All new patients should be discussed up front with the transplant centre.

Patients aged 25 years or older with Philadelphia positive ALL (up to age 65):

UKALL14 trial protocol. Imatinib should be added as soon as Ph +ve status is known. All new patients should be discussed up front with the transplant centre.

Patients aged 16-24 (up to 25th birthday) with Ph neg ALL:

Discuss with the TYA PTC

Patients aged 16-24 (up to 25th birthday) with Ph pos ALL:

Discuss with the TYA PTC

Adults whose age exceeds clinical trial protocol eligibility criteria

It should be remembered that the prognosis for patients 50-60 years and older is poor, particularly if there are other poor prognostic features (e.g. Ph+ve/ t(4;11)). A 'step-down' approach in intensity is suggested as follows:

1. *Fit, informed and willing:* consider a UKALL XII-like schedule in this circumstance but note the above cautions.
2. *Less fit, older or uncertain:* a less intensive schedule is appropriate. Induction with 2 doses of daunorubicin, weekly vincristine x 4, asparaginase and prednisolone (similar to the previous UKALL Xa schedule) is effective and may be followed with a consolidation block or simply standard maintenance at the clinician's discretion. CNS prophylaxis is with serial LPs only.
3. *Elderly or frail:* Vincristine x4 (1mg) and prednisolone followed by standard maintenance is simple. CNS prophylaxis may be considered on a case-by-case basis, and would be with serial lumbar punctures following the completion of the vincristine phase.

11.4.5 Treatment of primary refractory disease

This will be defined following second phase induction in UKALL14 regime or equivalent time point in other treatments.

NB: See below for a discussion of the use of Imatinib in Ph+ve cases.

Refractory disease has a dismal outlook with no schedule being clearly optimal.

The following may be considered:

- HyperCVAD
- FLAG
- High dose Ara-C schedules
- FLAG-Ida
- with Cytarabine as in paediatric practice (funding approval required).
- Rituximab addition for B-ALL (funding approval required).
- Alemtuzumab for T-ALL (funding approval required).
- Nelarabine for T cell ALL as a bridge to bone marrow transplantation (funding approval required).
- Dasatinib for patients with Ph +ve ALL with resistance or intolerance to prior therapy including imatinib (funding approval required).

11.4.6 Treatment of ALL relapsing after CR (Fielding, Richards et al. 2007)

If there is still curative intent then transplant options will be considered if possible and the patient should be discussed with the transplant centre prior to a decision to give further treatment as this may influence the choice of therapy.

Consider salvage regimen such as:

- HyperCVAD/High dose Methotrexate and Cytarabine
- FLAG
- High dose Ara-C schedules
- FLAG-Ida
- Alemtuzumab (funding approval required).
- Clofarabine with Cytarabine as in paediatric practice (funding approval required) for patients in whom the intent is to use treatment as a bridge to bone marrow transplantation.
- Rituximab addition for B-ALL (funding approval required).

CNS prophylaxis in the form of intrathecal therapy with 12.5 mg MTX on day 2 and 8 with each course of HyperCVAD. Use of autologous PBSCs collected in first CR may depend on the duration of remission.

NB: See below for a discussion of the use of Imatinib / dasatinib in this setting for Ph+ve cases.

These cases need discussion at an MDT incorporating transplant advice (see above).

Relapse has a very poor prognosis, particularly if it occurs less than a year from treatment end. If there is no transplant option then further chemotherapy can be considered as for refractory cases (see above).

Monotherapy in relapsed/refractory cases can achieve CRs in up to a third of patients although these are not durable. Tyrosine kinase inhibitors (imatinib / dasatinib) can be a useful agent in re-establishing short term remission prior to transplant. Post transplant relapses can also be managed in this way. The place of imatinib or dasatinib in these circumstances should be discussed at an appropriate MDT and funding approval is required. Dasatinib appears to be more effective and should be first choice. CNS prophylaxis must be considered in the context of the treatment schedule agreed at the MDT.

11.4.6.2 Treatment of Philadelphia +ve ALL with T315I mutation

Patients with Philadelphia +ive ALL with T315I mutation may be considered for ponatinib (funding approval required)

11.4.7 CNS leukaemia at diagnosis

Refer to CNS guidelines and follow protocol. NB Liposomal cytarabine IT (Depocyte) may be considered for the treatment of leukaemic / lymphomatous meningitis in patients not receiving systemic high dose treatment.

11.4.8 Special issues in antimicrobial prophylaxis

Refer to Kent & Medway – Cancer Guidelines for the antimicrobial management of neutropenia.

NB: There is a drug-drug interaction between itraconazole and vincristine which can lead to increased vincristine neurotoxicity.

11.5 Hairy Cell Leukaemia

11.5.1 Presentation

- Cytopenia
- Splenomegaly (60-70%)
- Hepatomegaly (40-50%)
- Occasionally lymphadenopathy – (more usually intra-thoracic / intra-abdominal rather than peripheral)
- Arthritis / arthralgia
- Rashes / erythema nodosum
- Vasculitis / pulmonary infiltrates (rare)
- Ascites / pleural effusions (rare)
- Aseptic meningitis / nerve compression (rare)

11.5.2 Investigations

- FBC and film:
 - Cytopenia
 - Monocytopenia (in classical HCL not HCLv)
- U+E / LFTs / Serum electrophoresis + Immunoglobulins
- Peripheral blood immunophenotyping of classical HCL:
 - B cell markers CD19+ / CD20+ / CD22+ / FMC7+
 - Smlg+ strong (50% are IgG)
 - CD5 neg / CD23 neg
 - Specific hairy cell markers
 - CD11c+
 - CD25+
 - CD103+
 - (HC2+)
 - In hairy cell leukaemia – Score 3-4
- Bone marrow:
 - Aspirate (may be difficult / dry tap due to fibrosis)
 - Trepine: Immunohistochemistry – L26 (an epitope on CD20) - good for detecting residual disease post treatment
- Imaging:
 - Consider US abdomen – to determine spleen and liver size
 - Consider CXR – to exclude infection / autoimmune phenomena / LN
 - Consider CT abdomen if suspect lymphadenopathy or if atypical HCL

11.5.3 Treatment of HCL

Depends upon age of patient, severity of symptoms and degree of cytopenia

- Watch and wait – if minimal splenomegaly, mild cytopenia, significant co-morbidity or very elderly
- Treat if significant symptoms or cytopenia e.g.
 - Anaemia
 - Neutrophils $< 1.0 \times 10^9/L$
 - Platelets $< 100 \times 10^9/L$

11.5.3.1 Chemotherapy

Note that responses can be slow and may continue even after the end of chemotherapy

First choice: **Pentostatin (2' –Deoxycoformycin) or Cladribine (2-Chlorodeoxyadenosine)** (iv or sub cutaneously)

- Consider the addition of Rituximab at presentation if very severe neutropenia ($\leq 0.2 \times 10^9/L$). (Funding approval required).

Alternative regimen: **alpha-interferon**

Indicated in:

- Severe cytopenia at presentation
 - If good response treat for 2-4 months until counts improve
 - Then treat with pentostatin / cladribine
- Sepsis
- Previous good response with α -interferon
- Renal failure

11.5.3.1.2 Relapsed/Refractory Disease

- Rituximab +/- chemotherapy for patients previously treated with cladribine and pentostatin. If used in combination with Pentostatin or Cladribine following first-line use of the alternate regimen, funding approval is required.

11.5.4 Splenectomy

- Consider in patients with minimal marrow infiltration and significant splenomegaly
- Consider in patients refractory to other treatments
- Indicated in splenic rupture
- Patients would require vaccination pre-splenectomy
- Penicillin / erythromycin prophylaxis
- Post splenectomy, recommended to wait at least 6 months before considering other therapy

11.6 References for HCL

BCSH guidelines on diagnosis and therapy – Hairy cell leukaemia Feb 2000

Hayden et al. A review of treatment options in hairy cell leukaemia

British Journal of Cancer Management 2004 Vol 1 No 2 pp12-15

Dearden et al. Long term follow-up of patients with hairy cell leukaemia after treatment with pentostatin or cladribine. Br J Haematology 1999; **106**: 515-519

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11.7 Management Plan for CLL/Lymphocytic NHL

These guidelines are to be used in conjunction with the BCSH and CLL Forum guidelines. (Oscier, Fegan et al. 2004)

11.7.1 Diagnostic Criteria

This is a chronic leukaemia of CD5+ B-cells. The term includes cases presenting as lymphadenopathy, formerly known as small lymphocytic leukaemia.

Typical cases

Consists mainly of small lymphocytes with clumped heterochromatin, although considerable morphological variation can occur.

Lymph nodes show a diffuse infiltrate usually with pseudofollicle formation.

Immunophenotype: CD5+, CD19+, CD20wk, CD79bwk, FMC7-, weak slg (slgM+/slgD+ or slgM-/slgD+)

Patients with circulating peripheral blood B-CLL counts of $<5 \times 10^9/l$ and no lymphadenopathy or splenomegaly are termed "monoclonal B-lymphocytosis (CLL phenotype)"

Variants:

CD23-, bcl-1/t(11;14) negative. This is an adverse prognostic group.

Solitary lymph node disease is very rare.

11.7.2 Prognostic factors (BSCH guidelines, BJH 2004)

Factor	Low risk	High risk
Gender	Female	Male
Clinical stage	Binet A Rai OI	Binet B or C Rai II, III, IV
Lymphocyte morphology	Typical	Atypical
Pattern of marrow trephine infiltration	Non-diffuse	Diffuse
Lymphocyte doubling time	>12 months	<12 months
Serum markers*	Normal	Raised
CD38 expression	<20-30%	>20-30%
Genetic abnormalities	None Del13q (sole)	Del 11q23 Loss/mutation of p53
IgVH gene status	Mutated	unmutated

* **Serum markers** These include $\beta 2$ microglobulin, lactate dehydrogenase (LDH), serum thymidine kinase and soluble CD23 (Knauf et al 1997; Hallek et al 1999; Di Raimondo et al, 2001; Schwarzmeier et al, 2002). All have been shown to predict progression and survival in Binet stage A patients, but their current value is currently limited either by the lack of a standard assay method, variable cut-off points between series or the lack of validation in a prospective study.

Essential investigations

- Full blood count
- Immunophenotyping of the peripheral blood
- Direct antiglobulin test (DAT) and reticulocyte count
- Serum immunoglobulins
- Renal and liver biochemistry (including urate and calcium levels)
- Calculation of Binet stage

Other recommended investigations

- Bone marrow aspirate and trephine biopsy is indicated in all of the following:
 - Phenotypically atypical CLL
 - For investigation of cytopenias in CLL
 - In patients for whom treatment is being considered
- Lymph node biopsy is indicated if:
 - The diagnosis is uncertain from the peripheral blood and bone marrow examinations.
 - To assess localized bulky lymphadenopathy to exclude transformation
- CT-scans/US
 - If the presence of splenomegaly is uncertain on physical examination
 - To assess lymphadenopathy prior to therapy
- Prognostic markers (FISH and VH mutation frequency) for those presenting with atypical features, advanced stage and young patients. It is advisable to check p53 status prior starting treatment as the presence of p53 (17p) deleted disease entails refractoriness to chemotherapy and need for allogeneic transplantation in fit patients once in remission.

11.8 Management of CLL

All newly diagnosed patients with CLL should have their management defined by a formal Multi-Disciplinary Team Meeting discussion.

11.8.1 Monoclonal B-lymphocytosis (CLL phenotype) – MBL-CLL

MBL-CLL is defined as the presence of a B-cell clone that has a CLL immunophenotype but at a level too low to meet the current criteria for the diagnosis of CLL ($<5 \times 10^9/l$) and with no lymphadenopathy or organomegaly (Marti, Rawstron et al. 2005). These patients have a very low risk of developing progressive disease and very few will eventually require therapy for CLL.

It is recommended that individuals with MBL-CLL are assessed clinically for symptoms potentially related to their disorder and for lymphadenopathy or organomegaly. They should have their blood counts monitored every 3 to 6 months in the first year and, if stable, annually thereafter. The regular follow-up can be performed in the local haematology clinic or by the patient's general practitioner.

11.8.2 Early stage (Binet's stage A) CLL

Treatment is not indicated for patients with early stage CLL regardless of the prognostic markers at presentation. There is currently no evidence to suggest that intervening at an early stage is beneficial even in poor risk CLL. However the likelihood of CLL progressing to therapy is related to the prognostic markers and the frequency of follow-up should be determined amongst other factors by the prognostic variables.

Patients with good risk CLL (isolated 13q14 deletion, mutated immunoglobulin genes) should be monitored every 3 to 6 months in the first year and, if the disease remains stable, annually thereafter. The regular follow-up can be performed in the haematology clinic or may be organised in primary care.

Patients with CLL with adverse prognostic features should be monitored every 3 months in the haematology clinic. Only after a period of time with stable disease should the intervals between patient's follow-up visits be extended.

11.8.3 Advanced stage CLL requiring therapy

Indications for initiating therapy

The indications for treatment recommended by the NCI sponsored working group (Cheson, Bennett et al. 1996) are as follows:

- Progressive marrow failure due to bone marrow infiltration by CLL
- Haemoglobin <10 g/dl
- Platelets <100 x 10⁹/l
- Massive or progressive lymphadenopathy (cluster >10cm diameter)
- Massive (>6cm below costal margin) or progressive splenomegaly
- Progressive lymphocytosis
- >50% increase over 2 months
- lymphocyte doubling time <6 months
- Systemic symptoms
- Weight loss >10% in previous 6 months
- Fever >38°C for >2 weeks
- Extreme fatigue
- Severe night sweats
- Autoimmune cytopenias which are poorly controlled by corticosteroids

11.8.4 Initial therapy for advanced CLL

Outside of trial:

Chlorambucil and fludarabine are both licensed for the first-line therapy of CLL. Fludarabine

monotherapy as first-line therapy results in higher response rates and prolonged progression-free survival compared to chlorambucil but does not result in an improved overall survival. The combination of fludarabine with cyclophosphamide results in higher response rates and prolonged progression-free survival compared to fludarabine monotherapy. (Eichhorst, Busch et al. 2003; Flinn, Kumm et al. 2004;

Catovsky, Richards et al. 2005). The follow-up of the key trials comparing fludarabine to FC is not mature enough to address the question of overall survival. FC has several advantages over fludarabine alone which include:

- lower incidence of autoimmune haemolytic anaemia
- lower cost (due to lower dose of fludarabine used in FC)
- higher response rates and prolonged progression-free survival

FCR has been shown to result in prolonged progression-free and overall survival (German CLL 4 study) and is now NICE approved. This is particularly evident in ATM deleted and good risk disease and in those who achieve MRD status. It is not significant over FC alone in poor risk disease however.

Recommendations for initial therapy in CLL:

All patients should be considered for entry into clinical trials.

- In patients without significant co-morbid conditions and who are <70 years of age the combination of **fludarabine plus cyclophosphamide plus rituximab (FCR)** should be considered standard first line therapy. (N.B. Patients with a high tumour burden or with a high number of lymphocytes ($\geq 25 \times 10^9/l$) who may be at higher risk of especially severe cytokine release syndrome, should only be treated with extreme caution. These patients should be very closely monitored throughout the first infusion. The Rituximab dose should be a split dosing over two days (100mg day 1, balance of dose day 2) until the white cell count drops to $< 25 \times 10^9/l$. Fludarabine plus cyclophosphamide may be considered as an alternative. The use of FCR Lite is currently being investigated for the older age groups but cannot be recommended as standard as it remains investigational.
- **Bendamustine** is recommended as an option for the first line treatment of CLL (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate (NICE TA 216, 2011). Addition of Rituximab (funding approval required) appears to improve responses (including CR) and progression free survival compared to R-Chlorambucil (MaBLE preliminary results, in press).
- **Alemtuzumab** with methyl-prednisolone or Dexamethasone is recommended for patients with previously untreated 17p deleted (p53 mutated) B-cell CLL. Alemtuzumab should also be considered for the first line treatment of T-cell prolymphocytic leukaemia.
- **Chlorambucil** preferably with Rituximab (funding approval required) is an option for elderly patients and those with significant co-morbid conditions.

Transplant options should be discussed with the transplant centre after initial or 2nd line treatment particularly in 17p deleted cases.

11.8.5 Relapsed but not refractory CLL (fludarabine-sensitive relapse)

Patients should be considered for entry into a clinical trial.

Fludarabine plus cyclophosphamide plus rituximab (FCR) should be considered for patients with relapsed CLL unless the patient has had rituximab before, or they have had fludarabine before and did not respond to it or relapsed within 6 months of treatment (NICE TA 193, 2010).

Patients with relapsed but not refractory CLL who are not eligible or decline entry into a trial should be considered for re-treatment with the same therapy (except FCR) as long as their initial remission was at least a year from the end of therapy. If the initial therapy was fludarabine alone then it is reasonable to re-treat with FC (see above).

Alemtuzumab should be considered for the treatment of relapsed CLL (with or without 17p deletion).

Bendamustine is licensed for the treatment of relapsed refractory low grade B-cell lymphoma including CLL and could be used with or without Rituximab (funding approval required). Alemtuzumab may be considered for the second line treatment of T-cell prolymphocytic leukaemia.

11.8.6 Fludarabine-refractory CLL

The prognosis for patients with fludarabine-refractory CLL treated with conventional therapy is very poor with a median survival of less than 12 months and a 5-year survival of approximately 10%. The incidence of p53 pathway abnormalities in these patients is extremely high and probably largely explains the resistance to conventional chemotherapeutic agents. The only licensed therapy for fludarabine-refractory CLL is Alemtuzumab. The response rates to Alemtuzumab are most influenced by the size of lymphadenopathy. The duration of remission and survival following Alemtuzumab are related to the depth of remission including whether minimal residual disease is eradicated. The following approaches are indicated for patients with refractory CLL who are considered suitable for intensive treatment:

Patients with predominantly blood and marrow disease with relatively small lymph nodes could be treated with Alemtuzumab alone for 12 weeks (Moreton, Kennedy et al. 2005). High dose methyl prednisolone (1g/m²/day for 5 days every 4 weeks) or Dexamethasone (40mg daily for 4 days every 4 weeks) addition increases efficacy in patients for whom high dose steroids are not contra-indicated. The aim of therapy should be to eradicate detectable minimal residual disease from the marrow. Fit patients should then be considered for allogeneic transplantation.

The following alternative therapies may be considered:

- Rituximab +/- high dose methylprednisolone
- Chloramucil (if not used previously)
- Lenalidomide (funding approval required)
- Thalidomide
- Investigational biological therapy

11.8.7 Fludarabine and Alemtuzumab refractory CLL

- Thalidomide with or without steroids
- Ofatumumab may be considered in the following indications (funding approval required):
 - 2nd or 3rd line treatment for patients refractory to treatment with Fludarabine combination and/or Alemtuzumab OR treatment with Fludarabine combination and/or Alemtuzumab contra-indicated

11.8.8 Allogeneic stem cell transplantation

CLL is an incurable disease by conventional treatment approaches. However there is a significant graft versus-CLL effect and long-term disease free survival is achievable following allogeneic stem cell transplantation. Patients who are possible candidates for allogeneic stem cell transplantation should be discussed with the transplant centre with due consideration of treatment related morbidity and mortality. Patients are generally only considered for allogeneic transplantation if they have poor-risk disease either according to biological characteristics of their CLL or because they have fludarabine-refractory disease.

11.8.9 Richter's Transformation

This is high grade transformation of CLL with aggressive behaviour, high CNS involvement risk and poor outcome. Treatment is as for DLBL (R-CHOP) with CNS prophylaxis (see CNS guidelines). Consider NCRI study (CHOP Ofatumumab) and transplant option with transplant centre.

11.9 CML

11.9.1 Investigations at Diagnosis

Before initiation of treatment:

- Full history including any occupational exposure to potential carcinogens and family tree.
- Physical examination including a measure of the size of the liver and spleen below the costal margins, height & weight.
- Full blood count and manual differential.
- Bone marrow aspirate and trephine biopsy. Samples for cytogenetic analysis and cell banking.
- Immunophenotyping of peripheral blood and BM if accelerated phase or blast crisis.
- Peripheral blood PCR analysis for BCR-ABL transcripts.
- Peripheral blood for tissue banking and serum for proteomics (research).
- Consider fertility issues if patient is of childbearing age.
- Calculate the Sokal and Hasford scores.

If the patient is a potential transplant candidate and a chronic phase leukapheresis is being considered:

- Virology including Hepatitis B & C, HIV, HTLV, CMV status

If allogeneic HSCT is being considered:

- HLA typing of patient and siblings.
- Consider VUD search.

Register the patient with local/regional CML patient registry.

11.9.2 WHO criteria for the definition of phases of CML¹

Chronic Phase

- Absence of other criteria suggestive of accelerated or blastic phase

Accelerated Phase

- Blasts 10-19% in bone marrow or peripheral blood.
- Peripheral blood basophils $\geq 20\%$
- Persistent thrombocytopenia ($<100 \times 10^9/l$) unrelated to therapy, or persistent thrombocytosis ($>1000 \times 10^9/l$) unresponsive to therapy.
- Increasing spleen size and increasing WBC count unresponsive to therapy
- Cytogenetic evidence of clonal evolution

Blastic Phase

- Blasts in peripheral blood or bone marrow $\geq 20\%$.
- Extramedullary blast proliferation
- Large foci or clusters of blasts in the bone marrow biopsy.

Patients who are classified initially in accelerated phase should be reassessed and reclassified when the counts have been controlled. Megakaryocytic proliferation occurring in sizeable sheets and clusters associated with marked reticulin or collagen fibrosis and/or severe granulocytic dysplasia should be considered as suggestive of AP-CML.

AIM: to achieve a complete molecular response and potential cure

Eligible patients in accelerated phase or blast phase CML should be considered for allografting, following treatment with imatinib/dasatinib/nilotinib/novel agents/intensive chemotherapy. Current evidence suggest that the responses to TKIs in these groups are not durable²⁻⁵. There is no evidence at present that pre-treatment with imatinib increases transplant-related mortality^{6,7}.

Some young patients in Chronic Phase CML with a suitable sibling donor may be considered for upfront allografting. This decision should be taken on an individual patient basis.

Some young patients in Chronic Phase CML with a suitable VUD donor may be considered for upfront VUD allografting. This decision should be taken on an individual patient basis.

11.9.4 First line therapy with imatinib or nilotinib: see flow charts

AIM: to achieve at least a durable complete cytogenetic response

The aim of tyrosine kinase inhibitor(TKI) therapy for CP-CML should be to achieve at least a complete cytogenetic response (CCyR). There no statistical difference between a good complete cytogenetic response (CCyR) (>2 log reduction in bcr-abl) and a major molecular response (MMR)(>3 log reduction in bcr-abl) in terms of progression free survival⁸.

Therapy with imatinib should be initiated at a dose of 300 to 400 mg/day. Doses below 300mg daily may not achieve sufficient intra-cellular concentrations to be effective and not be routinely prescribed⁹.

Patients receiving imatinib or nilotinib should have:

1. Full blood cell count, renal and liver function weekly for the first 4 weeks, then every 2-3 weeks until a Complete Haematological Response (CHR) and every 4-12 weeks thereafter.
2. Real time quantitative PCR for BCR-ABL every 3 months on peripheral blood.
3. Bone marrow aspirate and trephine biopsy with cytogenetics every 6 months until the patient reaches CCyR. Patients in confirmed CCyR (2 consecutive CCyR 6 months apart), should have bone marrow examinations at once every 12-18 months.
4. In potential transplant candidates, a Philadelphia negative leukapheresis and cryopreservation of stem cells may be considered again at this stage. However, patients who have achieved a good CCyR or MMR are not likely to require these cells⁸.
5. If the patient becomes neutropenic (neutrophils < $1.0 \times 10^9/l$) or thrombocytopenic (platelets < $50 \times 10^9/l$), imatinib should be interrupted. Restart when neutrophils are > $1.5 \times 10^9/l$ (if neutropenic) or platelets > $75 \times 10^9/l$ (if thrombocytopenic). Imatinib can then be reinstated at 400mg daily after a first episode of neutropenia/thrombocytopenia but reduced to 300mg after a second episode. Doses of less than 300mg daily should not routinely be prescribed
6. Support with G-CSF (105µg, 263µg or 300µg one to three times per week) may be considered for all patients who do not tolerate imatinib because of neutropenia and/or thrombocytopenia.
7. Non-haematological toxicity may be managed symptomatically, and with gradual dose re-escalation in the majority of patients.
8. Please see SmPC for other prescribing information and potential drug interactions

Haematologic response	Cytogenetic response	Molecular response
Complete: Platelet count $<450 \times 10^9/l$; WBC $< 10 \times 10^9/l$; differential without immature granulocytes and with less than 5% basophils; nonpalpable spleen	Complete: Ph 0% Partial: Ph 1-35% Minor: Ph 36-65% Minimal: Ph 66-95% None: Ph $> 95\%$	“complete” indicates transcript nonquantifiable and nondetectable Major : ≤ 0.10 (int scale)

Time	Failure	Suboptimal	Warnings
Diagnosis	NA	NA	high risk; del9q+; ACAs in Ph + cells
3 months	no HR	less than CHR	
6 months	less than CHR; Ph $>95\%$	Ph $>35\%$	
12 months	Ph $>35\%$	less than CCyR	less than MMR
18 months	less than CCyR	less than MMR	
Anytime	loss of CHR; loss of CgR	ACA; loss of MMR	rise in transcript levels; OCA in Ph neg cells

HR, haematological response; CHR, complete haematological response; CCyR, complete cytogenetic response; CgR, cytogenetic response; MMR, major molecular response; ACA, additional cytogenetic abnormalities; OCA, other cytogenetic abnormalities

- Failure implies that the patient should be considered for an alternative treatment plan.
- Suboptimal response implies that the patient may still have a substantial benefit from continuing imatinib treatment but that the long-term outcome is not likely to be optimal, so the patient may be considered for other treatment plans.
- Warnings imply that the patient should be monitored very carefully and may become eligible for other treatments.
- Until the International scale is fully adopted, a MMR is defined as a greater than 3 log reduction from the laboratory baseline (bcr-abl :abl %) and not the individual patient baseline ¹¹.

BCR-ABL analysis at 3 months to assess response.

“Failure” on imatinib and cause for change of therapy is:

- At three months, greater than 10% BCR-ABL transcript level (International Scale) or less than partial cytogenetic response
- At 12 months, lack of complete cytogenetic response (0% Ph+ bone marrow metaphases).
- At 18 months, regardless of which TKI the patient had started on or been switched to, less than complete cytogenetic response is defined as failure—the guidelines recommend switching to an alternate second-generation TKI.

There is no longer a six-month intervention time point.

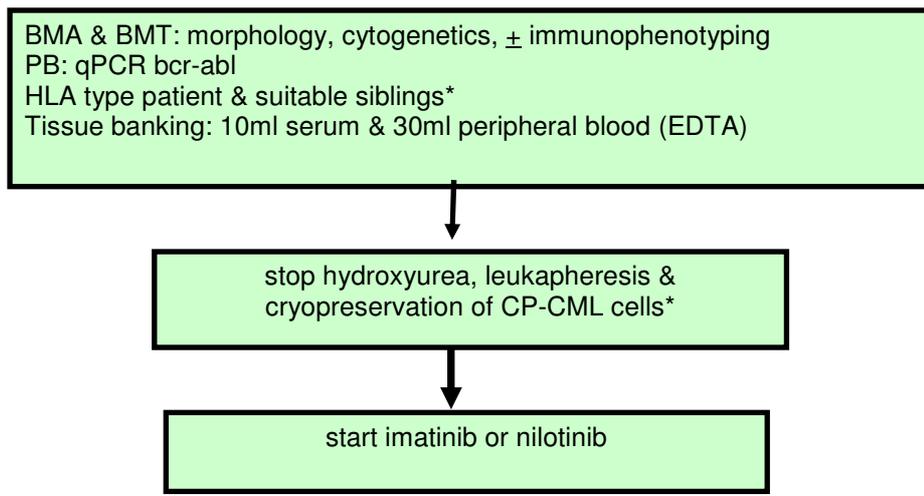
When “failure” is recognized, as defined above:

- Patients should be evaluated for patient compliance and drug interactions.
- Mutational analysis should be considered.

- If prior therapy has been imatinib, switching to nilotinib is recommended (rather than continuation or escalation of imatinib). And, if prior therapy is either dasatinib or nilotinib, the alternative agent is recommended (funding approval required). If patients are intolerant to nilotinib as a 2nd line treatment, dasatinib may be considered (funding approval required). NB Bosutinib is available through the NCDF for patients who are refractory to nilotinib or dasatinib.
- Patients should be evaluated for allogeneic hematopoietic stem cell transplant, depending on response to TKI therapy, and also considered for participation in clinical trials.

Patients who meet the ELN criteria for suboptimal response at six and 12 months—minor cytogenetic response at six months and partial cytogenetic response at 12 months—should be monitored closely, and may benefit from alternate treatment options, although the Guidelines make no specific treatment recommendation.

Ph' + CML, 1st Chronic Phase



*potential transplant candidates only

Eligibility

1. Imatinib intolerant

- a. Grade III to IV non-haematological toxicity persisting despite optimal supportive measures.
- b. Some grade II non-haematological toxicities persisting, 1 month or recurring >3 times with requirement for dose reduction or discontinuation, despite optimal supportive measures.

2. Imatinib resistant

See section 6.4.1

Note: Refer to nilotinib registration form for approved indications.

Dasatinib should be considered as second line treatment of chronic, accelerated or blast phase CML in patients with refractory or significant intolerance to imatinib, and who are intolerant of nilotinib (funding approval required).

Exclusions

1. Demonstrated presence of T315I abl tyrosine kinase domain mutation.
2. Uncontrolled of significant cardiovascular disease.
 - a. uncontrolled angina
 - b. MI within 6 months
 - c. congestive cardiac failure within 6 months
 - d. diagnosed or suspected long QT syndrome
 - e. history of significant ventricular arrhythmias
 - f. prolonged QTc >450 ms
 - g. 2nd or 3rd degree heart block
 - h. heart rate <50 bpm on ECG
3. Other exclusions/cautions as in the respective SPCs.

11.9.5.1 Dose of 2nd generation TKIs

The current recommended dose for dasatinib for patients with chronic phase CML is 100mg daily²¹. The current recommended dose of nilotinib is 400mg bd.

11.9.5.2 Assessment and duration of therapy with 2nd generation TKIs

In patients **resistant** to imatinib, dasatinib achieved a complete cytogenetic response rate of approximately 40%, compared with 16% in patients escalated to 800mg imatinib after a median follow-up of 15 months. Progression free survival favoured dasatinib²². Imatinib **intolerant(30%) or resistant(70%)** patients treated with nilotinib achieved 34% complete cytogenetic response after a median duration of treatment of 247 days²³.

Assessment of CP-CML patients on dasatinib and nilotinib should be according to the schedule defined for imatinib. Failure defined at 6 months should trigger a switch to an alternative treatment plan.

For accelerated and blast crisis patients, Insufficient data available currently, but would not be unreasonable to suggest absence of Major Haematological Response after 120 days of therapy for AP and BC patients (2x median time to response) should trigger a critical review of therapy. Note however that the median duration of response for lymphoid blast crisis and Ph positive ALL to dasatinib is less than 4 months, and myeloid BC less than 6 months²⁴.

11.9.6 Refractory Chronic phase, accelerated phase, or blast crisis CML or significant intolerance to dasatinib/nilotinib

Patients who are refractory to nilotinib or dasatinib or have significant intolerance may be considered for bosutinib (funding approval required).

11.9.7 Treatment of CML with T315I mutation

Patients with chronic, accelerated or blast phase CML with T315I mutation may be considered for ponatinib (funding approval required)

11.9.8 References for CML

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12.0 Acknowledgements

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13.0 Glossary

Acronyms in common usage throughout Kent & Medway - Cancer documentation:

CNB	Cancer Network Board
CYP	Children & Young People (in relation to the IOG)
DCCAG	Diagnostic Cross Cutting Advisory Group
TSSG	Tumour Site Specific Group (DOG/NSSG/TWG)
DVH	Darent Valley Hospital
EK	East Kent
EKHUFT	East Kent Hospitals University Foundation Trust
HoP	High Level Operational Policy
IOSC	Improving Outcomes: A Strategy for Cancer
K&C	Kent & Canterbury Hospital, Canterbury, (EKHUFT)
KMCN	Kent & Medway Cancer Network
KMCRN	Kent & Medway Cancer Research Network
LSESN	London & South East Sarcoma Network
MFT	Medway Foundation Trust
MTW	Maidstone & Tunbridge Wells NHS Trust
NOG	Non Surgical Oncology Group (<i>Permanent oncologist sub group of the TSSGs with a specific responsibility for chemo/rad pathways and advice to the TSSG, Network and geographical locations on new drugs</i>)
PoC	Pathway of Care (<i>Network agreed disease site specific clinical guidelines</i>)
QEQM	Queen Elizabeth the Queen Mother Hospital, Margate (EKHUFT)
QoL	Quality of life
RAT	Research and Trial Group (<i>Permanent sub-group of the TSSGs with a specific responsibility for taking forward the clinical trials agenda</i>)
RMH	Royal Marsden Hospital
RNOH	Royal National Orthopaedic Hospital
QVH	Queen Victoria Foundation Trust Hospital East Grinstead
UCLH	University College Hospital London
WHH	William Harvey Hospital, Ashford (EKHUFT)
WK	West Kent
CCG	Clinical Commissioning Groups

14.0 Document Administration

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