Pan Birmingham NHS
Cancer Network

Guidelines for the Management of Chronic Lymphocytic Leukaemia (CLL)

Version History

Version	Date	Summary of Change/Process
2.0	08.05.08	Endorsed by the Governance Committee
2.1	16.02.11	Circulated at NSSG meeting
2.2	28.04.11	Comments received from Farooq Wandroo
2.3	15.06.11	Approved by Haematology NSSG Chair
2.4	29.07.11	Updated and revised by Fiona Clark, Haematology NSSG Chair
3.0	03.08.11	Reviewed and endorsed by Guidelines Sub Group

Date Approved by Network Governance	**August 2011**

Date for Review	**August 2014**

Changes between versions 2 and 3

- Updated information on patients who should be offered FCR (rituximab in combination with fludarabine and cyclophosphamide) if they are deemed to be fit to tolerate fludarabine.
- Updated information on Transplant in CLL - autologous transplant is not recommended as part of standard care in CLL.
- Section on Immunoglobulin Replacement added

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

a) The management of patients suspected of having CLL
b) The management of patients diagnosed with CLL

2. Guideline Background

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

2.2 The Haematology NSSG has agreed to continue follow the British Committee for Standards in Haematology (BCSH) Guidelines on the diagnosis and management of chronic lymphocytic leukaemia (2004), of which this document is a summary. At the time of writing the 2011 version of the BCSH guidelines were in draft, but were also consulted.

Guideline Statements

3. Referral

3.1 Patients with the following a blood count / film reported as suggestive of chronic leukaemia should be referred to the local haematology team.

3.2 Patients with a combination of the following should undergo an urgent blood count, film and Erythrocyte sedimentation rate (ESR):

- Fatigue
- Drenching night sweats
- Fever
- Weight loss
- Breathlessness
- Bruising / bleeding
- Recurrent infections
- Lymphadenopathy
- Splenomegaly

3.3 Patients should be referred using in the 2 week wait form (appendix 1) to their local haematology service.

4. Investigation and Diagnosis (*full details of each can be found in the BJHaem guideline[1] and revised BCSH guidelines soon to be published*)

4.1 Clinical examination and history should include the following:

a) family history
b) susceptibility to infection
c) significant co-morbid conditions
d) peripheral lymphadenopathy
e) hepatosplenomegaly
f) bulky intra abdominal lymphadenopathy

4.2 Patients suspected of having leukaemia should undergo the following:

a) full blood count
b) lymphocyte morphology
c) immunophenotyping
d) direct antiglobulin test
e) reticulocyte count
f) renal and liver biochemistry
g) serum immunoglobulins
h) chest x-ray
i) CMV, hep serology

4.3 In addition clinicians may require the following:

a) bone marrow aspirate and trephine biopsy
b) lymph node biopsy (especially when clinical suspicion for transformation)
c) cytogenetic/fluorescence insitu hybridisation analysis (especially for 17p and 11q)
d) CT and or ultrasound of the chest / abdomen

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

5. First Line Treatment

5.1 Generally, only patients with progressive stage A or stages B or C will require treatment.

5.2 All patients requiring treatment should be assessed for their ability to tolerate intensive therapies. Important factors to consider are age, performance status, and significant comorbidity.

5.3 Patients should be offered FCR (rituximab in combination with fludarabine and cyclophosphamide) if they are deemed to be fit to tolerate fludarabine.

5.4 For patients who are not thought to be fit to receive FCR chemotherapy, they may be offered bendamustine as per NICE guidance.

5.5 If fludarabine is contra-indicated or a palliative approach intended standard dose chlorambucil should be offered.

5.6 Patients should be encouraged to opt for trials offering chlorambucil or brendamustine in combination with anticd20 antibodies.

5.7 Patients suitable for an allogeneic transplant should be offered FCR, or alemtuzumab may be considered in 17p deletion, as initial treatment.

5.8 Alemtuzumab monotherapy is not recommended in untreated CLL however alemtuzumab may be considered as initial therapy for those patients who have 17p deletion.

6. Second Line and Subsequent Treatment

6.1 Relapse of patients post FC: Patients who relapse at least 2 years after initial response to non-rituximab containing chemotherapy like FC and have no T53 abnormality may be offered FCR chemotherapy or if they had received rituximab in inadequate doses in first line therapy (see NICE Guidance).

6.2 Relapse post chlorambucil: Patients who had shown initial response to chlorambucil may be offered further chlorambucil or CHOP chemotherapy if not suitable for FCR.

6.3 Relapse post FCR: Patients who relapse more than 3 years post FCR chemotherapy and have no acquired T53 abnormality may be offered further FCR if fit enough (**This does not have NICE approval and may have to be requested via the Cancer Drug Fund**).

6.4 Management of refractory and high risk CLL: Patients who are refractory to purine analogue based therapy or patients who have T53 abnormality who require treatment are considered to have high risk CLL.

6.5 Fludarabine refractory disease and T53 abnormality: For patients who are otherwise fit, alemtuzumab should be given to patients without bulky disease, who are refractory to FC or FCR or have T53 abnormality.

6.6 For unfit high risk disease: These patients may be offered conventional dose glucocorticoids or radiotherapy to bulky disease as palliation.

6.7 Treatment options for patients who fail alemtuzumab are limited. High dose glucocortocoids, are experimental agents like ofatumumab, lenalidomide and flavopiridol may be considered within a clinical trial.

7. Transplant in CLL

7.1 Autologous transplant is not recommended as part of standard care in CLL.

7.2 Allogeneic stem cell transplant may be offered as a consolidation therapy for all fit patients with high risk disease (fludarabine refractory/T53 abnormality) who have achieved remission. Where possible planning should allow this to be considered before their disease becomes treatment resistant.

8. Advanced or Progressive Disease

8.1 Splenectomy is indicated in patients with massive symptomatic splenomegaly and in refractory cytopenias.

8.2 Splenic radiotherapy may be offered to patients with symptomatic splenomegaly where splenectomy is contra indicated.

8.3 Low dose involved field radiotherapy may be offered to patients with large bulky nodal disease.

9. Treatment of Lymphomatous Transformation

9.1 Depending upon histological subtype, these patients may be offered standard regimens for primary diffuse large B-cell NHL or Hodgkin's lymphoma if deemed fit.

9.2 Younger patients who achieve a good response may be offered allogeneic stem cell transplantation.

10. Treatment of Autoimmune Complications

10.1 Autoimmune complications occur in 10 - 20% of patients with CLL. A bone marrow aspirate is required to confirm the diagnosis. AIHA or ITP should be treated before deciding whether therapy for CLL is needed.

10.2 The first line therapy is prednisolone, there are no standard recommendations for second line therapies. New TPO agonists are not recommended in CLL.

10.3 CLL treatement with rituximab containing regimen may be initiated to control recurrent or refratory AIHA/ITP.

11. Immunoglobulin Replacement

This may be considered in patients with low serum IgG level who have have experienced major or recurrent minor bacterial infections despite optimal antimicrobial prophylaxis.

12. Follow-up

12.1 Patients with stable stage A disease (especially elderly patients) should be discharged to primary care for follow up once a diagnosis has been made. These patients and their GPs should be informed of the signs/symptoms that suggest disease progression. They should have access to the haematology clinic within 2 weeks of consulting the GP for possible disease progression.

12.2 Most patients who have received chemotherapy will require further chemotherapy in the future and should be followed up at 3 - 4 month intervals in the haematology clinic. Those patients who have exhausted the chemotherapy options will require supportive care such as blood transfusions until they need to be referred to the palliative care team.

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

13. Palliative Care

Palliative care services will be made available to all patients as deemed appropriate by the MDT.

14. Clinical Trials

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

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

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

Monitoring of the Guideline

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

References

1 BCSH 2004. Guidelines on the diagnosis and management of chronic lymphocytic leukaemia BJHaem 125 p 294-317. www.bcshguidelines.com and BCSH guidelines for CLL 2011(Draft)
2 NICE 2005 Referral Guidelines for Suspected Cancer www.nice.org.uk
3. NICE 2009, Guidelines on the use of Rituximab for the first line treatment of CLL www.nice.org.uk
4. NICE 2010, Guidelines on the use of Rituximab for relapsed CLL, www.nice.org.uk
5. NICE Feb2011, Guidelines on the use of bendamustine as an alternative to FCR for the first line treatment of CLL, www.nice.org.uk
6. IWCLL, 2008 Guidelines for Diagnosis and management of CLL, Blood, Jan 2008

Author of version 3

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Authors of versions 1 and 2

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2 Farooq A Wandroo Consultant Haematologist

Approval Signatures

Pan Birmingham Cancer Network Governance Committee Chair

Name: Doug Wulff

Signature  Date August 2011

Pan Birmingham Cancer Network Manager

Name: Karen Metcalf

Signature  Date August 2011

Network Site Specific Group Clinical Chair

Name: Fiona Clark

Signature  Date August 2011

Appendix 1 – 2 week wait referral form

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URGENT REFERRAL FOR SUSPECTED HAEMATOLOGY CANCER

If you wish to include an accompanying letter, please do so. **On completion please FAX to the number below.** (Version 2.0)

These forms should only be used for suspected cancer and in conjunction with the NICE Referral Guidelines for Suspected Cancer, June 2005

Patient Details	**GP Details (inc Fax Number)**
Surname Forename D.O.B. Gender Address Postcode Telephone	
NHS No	**Date of Decision to Refer**
Hospital No	**Date of Referral**
Interpreter? Y / N First Language:	**GP Signature**

Relevant information: (Check as appropriate)

Symptoms/Signs:

Fatigue	☐	Drenching night sweats	☐	Fever	☐
Weight Loss	☐	Generalised itching	☐	Recurrent infections	☐
Bruising	☐	Breathlessness	☐	Lymphadenopathy	☐
Bone Pain	☐	Alcohol-induced pain	☐	Persistent unexplained splenomegaly	☐

Additional Lymphadenopathy Features:

Lymph nodes increasing in size	☐	Lymph nodes greater than two cm in size	☐
Persistence for six weeks or more	☐	Widespread nature	☐
Associated splenomegaly, night sweats or weight loss	☐		

Investigations:

ESR	_____	Full Blood Count	_____
Blood film	_____	Clotting screen	_____
X-ray	_____	Liver/Bone profile	_____
Urea & Electrolytes	_____	Immunoglobulin/paraprotein	_____

Clinical Details:

History/Examination/Investigations……

Medication ……

For Hospital Use

Appointment Date Clinic Attending

Was the referral appropriate Yes No (if no please give reason)

HAEMATOLOGY CLINICS WITH RAPID ACCESS FACILITIES

Hospital	Tel	Fax
City and Sandwell	**0121 507 5805**	**0121 507 5075**
Good Hope	**0121 424 5000**	**0121 424 8952**
Heartlands and Solihull	**0121 424 5000**	**0121 424 8952**
Queen Elizabeth (UHBFT)	**0121 627 2485**	**0121 460 5800**
Walsall Manor	**01922 721172 ext 7110 or 7785**	**01922 656773**