Complete Summary

GUIDELINE TITLE

Guidelines on the diagnosis and management of chronic lymphocytic leukaemia.

BIBLIOGRAPHIC SOURCE(S)

Oscier D, Fegan C, Hillmen P, Illidge T, Johnson S, Maguire P, Matutes E, Milligan D, Guidelines Working Group of the UK CLL Forum, British Committee for Standards in Haematology. Guidelines on the diagnosis and management of chronic lymphocytic leukaemia. Br J Haematol 2004 May;125(3):294-317. [169 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- September 11, 2008, Rituxan (Rituximab): Genentech informed healthcare professionals of revisions to prescribing information for Rituxan regarding a case of progressive multifocal leukoencephalopathy (PML) leading to death in a patient with rheumatoid arthritis who received Rituxan in a long-term safety extension clinical study.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Chronic lymphocytic leukaemia

GUIDELINE CATEGORY

Diagnosis
Management
Treatment

CLINICAL SPECIALTY

Family Practice
Hematology
Internal Medicine
Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

The purpose of this guideline is to provide a rational approach to the diagnosis and management of patients with chronic lymphocytic leukaemia (CLL).

TARGET POPULATION

Patients with chronic lymphocytic leukaemia

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis

1. Blood count
2. Immunophenotyping
3. Additional investigations (direct antiglobulin test, reticulocyte count, renal and liver biochemistry (including urate levels), serum immunoglobulins, chest X-ray, bone marrow aspirate, trephine biopsy)

Treatment

1. Initial treatment
    - Fludarabine
    - Fludarabine and cyclophosphamide
    - Chlorambucil
2. Second line and subsequent treatment
    - Chlorambucil

- Fludarabine
- CHOP (cyclophosphamide, adriamycin, vincristine, prednisolone)
- Fludarabine and cyclophosphamide
- High dose methylprednisolone
- Alemtuzumab
- Rituximab plus fludarabine, with or without cyclophosphamide
- Autologous transplantation
- Allogeneic transplantation
- Splenectomy

3. Infection prophylaxis
    - Septrin, pentamidine (for patients receiving purine analogues or alemtuzumab)
    - Fluconazole (for patients receiving methylprednisolone)
    - Cytomegalovirus monitoring (for patients receiving purine analogues or alemtuzumab)
    - Intravenous immunoglobulin (for patients with hypogammaglobulinaemia)
4. Infection treatment
    - Broad spectrum antibiotics
5. Treatment of autoimmune cytopenias

MAJOR OUTCOMES CONSIDERED

- Response to therapy
- Adverse events
- Quality of life
- Survival

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Recommendations are based on a review of the literature using Medline/Pubmed searches under the heading, CLL, up to October 2003 and data presented at the American Society of Hematology in 2003 and at the 10th International Workshop on chronic lymphocytic leukaemia (CLL) in 2003. The results of meta-analyses and phase 3 studies that have been published or presented in abstract form are included.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Levels of Evidence

Ia Evidence obtained from meta-analysis of randomised controlled trials

Ib Evidence obtained from at least one randomised controlled trial

IIa Evidence obtained from at least one well-designed, controlled study without randomisation

IIb Evidence obtained from at least one other type of well-designed, quasi-experimental study

III Evidence obtained from well-designed, non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies

IV Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Treatment recommendations were influenced by current and proposed clinical trials in the UK and by guidance from the National Institute for Clinical Excellence (NICE).

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Grades of Recommendation

Grade A, evidence level Ia, Ib

Required at least one randomized controlled trial as part of the body of literature of overall good quality and consistency addressing specific recommendation

Grade B, evidence level IIa, IIb, III

Required availability of well-conducted clinical studies but no randomised clinical trials on the topic of recommendation

Grade C, evidence level IV

Required evidence obtained from expert committee reports and/or clinical experiences of respected authorities

Indicates absence of directly applicable clinical studies of good quality

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

A draft guideline was reviewed by members of the UK on chronic lymphocytic leukaemia (CLL) Forum, patient representatives, members of the British Society of Blood and Marrow Transplantation (BCSH) and a panel of approximately 60 UK haematologists. Their comments were incorporated where appropriate.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The levels of evidence **(I–IV)** and strength of recommendations **(A–C)** are defined at the end of the "Major Recommendations" field.

Diagnosis and Prognostic Factors

Diagnostic Investigations

Blood count

Current criteria for the diagnosis of chronic lymphocytic leukaemia (CLL) require a lymphocytosis of >5 x 10^9/l. Patients whose routine blood count shows a lower level of lymphocytosis may subsequently develop clinically significant CLL. Options for adult patients with a lymphocytosis of between 3 and 5 x10^9/l and lymphocyte morphology consistent with CLL include immunophenotyping or a follow-up blood count.

Immunophenotyping

Immunophenotyping should be performed in all cases requiring treatment and is of particular value in the following situations: (i) in cases with low lymphocyte counts to confirm the diagnosis of CLL and exclude reactive lymphocytosis; and (ii) in patients with atypical lymphocyte morphology to exclude other B- or T-cell lymphoproliferative disorders.

A recommended panel of monoclonal antibodies and scoring system for the diagnosis of CLL is shown in Table II of the original guideline document.

Management of CLL

Indications for Referral

Indications for referral to a haematology department include: symptomatic disease, the presence of lymphadenopathy or hepatosplenomegaly and the investigation of a lymphocytosis, particularly if the lymphocyte count is high or there is anaemia or thrombocytopenia. The subsequent management of these patients should be discussed at a multi-disciplinary team meeting.

The follow-up of patients seen initially in hospital, who do not require treatment, may be organized in primary care, hospital outpatients or via a homecare service depending on local resources and patient wishes. Asymptomatic elderly patients, with a slight lymphocytosis only, may be managed by primary care teams, providing indications for referral to a haematology department are clearly documented.

Communicating with Patients

Chronic lymphocytic leukaemia is characteristically a condition for which the natural history is measured in years and it is therefore particularly important that patients are able to establish a relationship and trust with the clinician managing their condition.

A frequent dilemma is whether to convey the diagnosis of CLL to an elderly asymptomatic patient with low count stage A disease diagnosed on a routine blood count. Anxiety generated by the use of the word 'leukaemia' can almost always be prevented by a clear and careful explanation of the benign nature of the condition. If a decision not to inform a patient is taken this must be very clearly documented to ensure that other health care workers do not subsequently impart the diagnosis without explaining its significance.

The majority of patients benefit from, and should be offered, information about CLL in general and about their specific management.

Indications for Treatment

The indications for treatment recommended by the National Cancer Institute (NCI) sponsored working group are shown in Table V of the original guideline document.

Assessment of Response

The criteria for assessing complete response (CR) or partial response (PR) to treatment recommended by the NCI working group are shown in Table VI of the original guideline document.

A Treatment Strategy for CLL

Before initiating treatment, consideration must be given to (i) patient-related factors, such as age, performance status, co-morbid conditions and patient wishes; (ii) disease-related factors, such as the severity of symptoms and the presence of adverse prognostic factors; and (iii) treatment-related factors including the degree and duration of response to prior treatments and contra-indications to, and side-effects from, particular treatment modalities. Pharmacoeconomic considerations (see Table VII of the original guideline document) are also important.

An important consideration on beginning treatment in CLL is whether to adopt a palliative approach and treat symptomatic disease with regimens causing minimal treatment-related toxicity, or to aim for prolonged disease-free survival in the hope that this will translate into superior overall survival.

Initial Treatment

Treatment of early stage CLL

Treatment of early stage disease with chlorambucil is not indicated (**grade A recommendation, level Ia evidence**).

Treatment of Advanced or Progressive Disease

Purine analogues

To prevent transfusion related graft versus host disease (GVHD), all patients treated with a purine analogue should receive irradiated blood products indefinitely thereafter.

Steroids

There is no evidence that prolonged treatment with low, intermediate or high-dose steroids is an effective initial treatment for CLL. However, it is recommended that patients with stage C disease should be given a short course of prednisolone before receiving chlorambucil (**grade C recommendation, level IV evidence**).

Summary of Recommendations for Initial Treatment

For the majority of patients who are ineligible for a transplant procedure and in whom there is no contraindication to fludarabine (severe renal impairment or an autoimmune cytopenia), entry into the MRC CLL4 study should be offered. This trial randomizes patients to either chlorambucil, fludarabine, or fludarabine and cyclophosphamide and assesses the value of prognostic factors and quality of life

issues as well as outcome. Both fludarabine and chlorambucil are options for patients who do not wish to enter the study.

Patients in whom fludarabine is contraindicated and for whom a palliative approach has been adopted should be treated with chlorambucil (**grade A recommendation, level Ia evidence**).

There is no survival advantage for including an anthracycline with chlorambucil in the initial treatment of advanced chronic lymphocytic leukaemia (CLL) (**grade A recommendation, level Ia evidence**).

Further studies using standard response criteria are required before high-dose chlorambucil can be recommended as an initial treatment for CLL (**grade C recommendation, level IV evidence**).

Where a patient is considered suitable for entry into the MRC CLL5 trial or for allogeneic transplantation, then an initial treatment, such as fludarabine or fludarabine and cyclophosphamide, which is likely to result in a complete or very good partial remission, should be chosen (**grade C recommendation, level IV evidence**).

Alemtuzumab is not recommended for untreated CLL (**grade B recommendation, level IIb evidence**).

Rituximab monotherapy is not recommended in untreated CLL (**grade C recommendation, level III evidence**).

Rituximab combined with fludarabine (with or without cyclophosphamide) requires further evaluation in untreated CLL (**grade B recommendation, level Ib evidence**).

Summary of Recommendations for Second Line and Subsequent Treatment

Patients who relapse after an initial response to low dose chlorambucil may be treated with a further course of chlorambucil (**grade B recommendation, level IIb evidence**).

Patients refractory to low dose chlorambucil should be treated with fludarabine. Cyclophosphamide, adriamycin, vincristine, prednisolone (CHOP) is an alternative treatment for patients unsuitable for fludarabine (**grade B recommendation, level IIb evidence**).

Patients who develop progressive disease more than 1 year after receiving fludarabine and whose CLL responded to fludarabine initially, may be treated again with fludarabine alone (**grade B recommendation, level IIb evidence**).

Patients who develop progressive disease within 1 year of previous fludarabine therapy may be treated with a combination of fludarabine and cyclophosphamide (**grade B recommendation, level IIb evidence**).

Patients who are refractory or become resistant to fludarabine currently have a poor prognosis. Therapeutic options include the following:

- High-dose methyl prednisolone is recommended as a treatment option for patients who are resistant to fludarabine, particularly in cases with bulky lymphadenopathy and/or p53 abnormalities (**grade B recommendation, level III evidence**).
- Alemtuzumab is licensed for and recommended in patients without bulky lymphadenopathy, previously treated with alkylating agents and refractory to fludarabine (**grade B recommendation, level IIb evidence**).
- Rituximab monotherapy is not recommended for previously treated CLL (**grade C recommendation, level IIb evidence**). Rituximab combined with fludarabine (with or without cyclophosphamide) may be effective in refractory CLL and warrants further evaluation in this setting (**grade B recommendation, level IIb evidence**).

Autologous transplantation should be considered for patients in complete or good partial remission who are able to withstand high-dose chemotherapy and total body irradiation (TBI). Autologous transplantation should be performed in the context of a randomized trial, such as the MRC CLL5 trial.

The possibility of an allogeneic transplant procedure should be considered for younger patients with good performance status who have been previously treated and have poor risk disease. Suitable patients should be discussed with a transplant centre at an early stage in their disease before the development of drug resistant disease for inclusion into a clinical research protocol (**grade B recommendation, level III evidence**).

Splenectomy may be beneficial in relieving symptomatic splenomegaly and in improving peripheral cytopenias secondary to hypersplenism or autoantibodies (**grade B recommendation, level IIa evidence**).

Management of Complications

Prophylaxis

Antibiotic therapy

Prophylaxis against *Pneumocystis carinii* with septrin or nebulized pentamidine should be administered routinely for all patients receiving purine analogues or alemtuzumab, and continued for a minimum of 6 months after stopping purine analogues or alemtuzumab (**grade C recommendation, level IV evidence**).

Prophylaxis against herpes zoster/simplex and fungal infections should also be considered for patients receiving purine analogues or alemtuzumab, particularly if there is a previous history of herpetic or fungal infection. Patients treated with high-dose methylprednisolone should receive prophylaxis against candidiasis with fluconazole.

Regular weekly monitoring with cytomegalovirus polymerase chain reaction (CMV PCR) testing should be performed in patients receiving alemtuzumab. A positive

quantifiable CMV PCR result is an indication for treatment with intravenous ganciclovir.

Intravenous Immunoglobulin (IVIG)

Patients with hypogammaglobulinaemia and recurrent bacterial infections, especially those in whom prophylactic antibiotics have proved ineffective, should be treated with prophylactic IVIG (**grade A recommendation, level Ib evidence**).

Treatment of Infections

Patients and their carers need to be educated about the risks of infection and the necessity to seek immediate medical attention as soon as suggestive symptoms occur. Patients with minor infections can be treated as outpatients, but those with major infections will require hospitalization and access to full resuscitation including respiratory support. As many infections are potentially life threatening, broad spectrum antibiotics covering the common likely pathogens should be started as soon as all essential cultures have been taken.

Autoimmune Cytopenias

It is recommended that patients with warm autoimmune hemolytic anemia (AIHA) or immune-mediated thrombocytopenia (ITP) are treated according to the protocols used for patients with idiopathic AIHA or ITP (**grade C recommendation, level IV evidence**). Autoimmune cytopenias developing following purine analogue therapy are frequently severe and may be fatal. The majority of patients who have developed AIHA post fludarabine have had recurrent haemolysis on re-exposure to fludarabine. There have been reports of small numbers of patients in whom fludarabine has been re-introduced successfully while patients are on ciclosporin A.

However, retreatment with a purine analogue cannot be recommended in a patient who has previously developed a purine analogue-related immune cytopenia (**grade B recommendation, level IIa evidence**).

Lymphomatous Transformation

No standard treatment can be recommended for Richter's transformation of CLL; existing clinical reports fail to identify consistently effective therapy (**grade C recommendation, level IV evidence**).

Definitions:

Levels of Evidence

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Grade A, evidence level Ia, Ib

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Grade B, evidence level IIa, IIb, III

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Grade C, evidence level IV

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CLINICAL ALGORITHM(S)

An algorithm, "Treatment options in chronic lymphocytic leukaemia (CLL)" is provided in the original guideline document.

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for most of the recommendations (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate management of chronic lymphocytic leukaemia (CLL), including control of disease, prevention of debilitating and life-threatening complications, improved quality of life, and prolonged survival

POTENTIAL HARMS

- Side effects of treatment (including treatment related infection) and treatment-related mortality.
- Purine analogues may produce anaemia, severe neutropenia, thrombocytopenia and severe infections
- Several studies have reported an association between auto-immune hemolytic anemia (AIHA) and treatment with purine analogues
- Ten per cent of patients develop cytomegalovirus (CMV) reactivation following treatment with alemtuzumab
- Disabling graft-versus-host disease (GVHD) following allogeneic transplantation can result in considerable reduction in quality of life.

CONTRAINDICATIONS

CONTRAINDICATIONS

High-dose methyl prednisolone (HDMP) is contraindicated in patients with an active gastric or duodenal ulcer and should be used with caution in patients with diabetes or heart failure.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

Whilst the advice and information contained in this guideline are believed to be true and accurate at the time of going to press, neither the authors nor the publisher can accept any legal responsibility or liability for any errors or omissions that may be made.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Oscier D, Fegan C, Hillmen P, Illidge T, Johnson S, Maguire P, Matutes E, Milligan D, Guidelines Working Group of the UK CLL Forum, British Committee for Standards in Haematology. Guidelines on the diagnosis and management of chronic lymphocytic leukaemia. Br J Haematol 2004 May;125(3):294-317. [169 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2004 May

GUIDELINE DEVELOPER(S)

British Committee for Standards in Haematology - Professional Association

SOURCE(S) OF FUNDING

British Committee for Standards in Haematology

GUIDELINE COMMITTEE

Guidelines Working Group of the UK chronic lymphocytic leukaemia (CLL) Forum

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available from the British Committee for Standards in Haematology Web site.

Print copies: Available from BCSH Secretary, British Society for Haematology, 100 White Lion Street, London N1 9PF, UK; E-mail: janice@b-s-h.org.uk

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on September 27, 2006. The information was verified by the guideline developer on October 25, 2006. This summary was updated by ECRI on January 12, 2007 following the U.S. Food and Drug Administration (FDA) advisory on Rituxan (Rituximab). This summary was updated by ECRI Institute on October 8, 2008 following the U.S. Food and Drug Administration advisory on Rituxan (rituximab).

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