



Complete Summary

GUIDELINE TITLE

Guidelines on the management of acute myeloid leukaemia in adults.

BIBLIOGRAPHIC SOURCE(S)

Milligan DW, Grimwade D, Cullis JO, Bond L, Swirsky D, Craddock C, Kell J, Homewood J, Campbell K, McGinley S, Wheatley K, Jackson G. Guidelines on the management of acute myeloid leukaemia in adults. London (UK): British Society of Haematology (BSH); 2005 May 23. 77 p. [202 references]

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.

- [January 24, 2008, Leukine \(sargramostim\)](#): Voluntary market suspension of the current liquid formulation of sargramostim, a granulocyte-macrophage colony-stimulating factor (GM-CSF), because of an upward trend in spontaneous reports of adverse reactions, including syncope (fainting). The lyophilized form of the drug is not affected. See the U.S. Food and Drug Administration (FDA) web site for more information.

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INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT

CATEGORIES

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SCOPE

DISEASE/CONDITION(S)

Acute myeloid leukemia (AML)

GUIDELINE CATEGORY

Diagnosis
Management
Treatment

CLINICAL SPECIALTY

Hematology
Obstetrics and Gynecology
Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To give an up-to-date overview of evidence-based and expert opinion-based optimum management of acute myeloid leukemia in the UK

TARGET POPULATION

- Adults with acute myeloid leukemia (AML)
- Pregnant women with AML

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis

1. Bone marrow aspirate
2. Trepine biopsy
3. Immunophenotyping (CD3, CD7, CD13, CD14, CD33, CD34, CD64, CD117, cytoplasmic myeloperoxidase (MPO))
4. Cytochemistry (MPO or Sudan Black, combined esterase)
5. Four colour flow cytometry.
6. Cytogenetics (with reverse transcription-polymerase chain reaction [RT-PCR] for AML1-ETO and CBFβ-MYH11 in non-acute promyelocytic leukemia (APL) and PML-RARA in suspected APL; fluorescent in situ hybridization [FISH])

Acute Myeloid Leukemia (AML) Treatment

1. Rasburicase (with chemotherapy for patients at risk of tumour lysis syndrome)

2. Younger adult patients
 - Participation in the current UK National Cancer Research Institute (NCRI) study (at present AML 15)
 - Daunorubicin and cytarabine induction chemotherapy
 - Low-dose cytarabine
 - Best supportive care (transfusion support and hydroxycarbamide)
3. Patients over 60
 - Participation in the current NCRI study, (at present Leukemia Research Foundation AML 14 (<http://www.aml14.bham.ac.uk>) or HOVON/SAKK AML43)
4. Pregnant women
 - Joint patient management with haematologist and obstetrician
 - Discussion of pregnancy termination
 - Chemotherapy
 - All-trans retinoic acid (ATRA)
5. Management of extra-medullary disease
 - Systemic antileukaemic chemotherapy
6. Transplantation in AML
 - Inform patient on advantages and disadvantages and long term side effects
 - Intensive consolidation chemotherapy
 - Allogeneic transplantation
 - Fertility preservation
7. AML in the elderly
 - Induction chemotherapy (daunorubicin [or an equivalent anthracycline] plus cytarabine)
 - Participation in clinical trial
 - Relapsed disease (gemtuzumab ozogamicin)
 - Palliative therapy (low-dose cytarabine)

Acute Promyelocytic Leukemia (APL) Treatment

1. ATRA
2. Treatment of coagulopathy
3. Treatment of ATRA syndrome (dexamethasone)
4. Patients with PML-RARA positive APL
 - ATRA and anthracycline-based chemotherapy, anthracycline-based consolidation therapy, entry into the NCRI AML trial (currently AML15)
5. Molecular monitoring of response
6. Relapsed disease
 - Arsenic trioxide (PML-RARA positive APL)

MAJOR OUTCOMES CONSIDERED

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

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The Pub Med, Cochrane and Medline databases in the English language were searched using the key words "acute myeloid leukaemia/leukemia, acute promyelocytic leukaemia/leukemia, stem cell transplantation with sub-headings anthracycline, pregnancy, disseminated intravascular coagulation, growth factors and quinolones from 1983-2005.

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

Classification of Evidence Levels

Ia Evidence obtained from meta-analysis of randomized controlled trials.

Ib Evidence obtained from at least one randomized controlled trial.

IIa Evidence obtained from at least one well-designed controlled study without randomization.

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 studies.

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

METHODS USED TO ANALYZE THE EVIDENCE

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

The recommendations were agreed using the Agree instrument (<http://www.agreecollaboration.org>).

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Classification of Grades of Recommendation

- A. Requires at least one randomised controlled trial as part of a body of literature overall good quality and consistency addressing specific recommendation. (**Evidence levels Ia, Ib**).
- B. Requires the availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation. (**Evidence levels IIa, IIb, III**).
- C. Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality. (**Evidence level IV**).

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

The recommendations were further reviewed by a Sounding Board of 100 haematologists representing adult practice in both teaching and district hospitals.

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

1. Bone marrow aspirate and trephine biopsy unless the peripheral blast count is high.
2. Immunophenotyping (CD3, CD7, CD13, CD14, CD33, CD34, CD64, CD117, cytoplasmic myeloperoxidase (MPO))
3. Cytochemistry (MPO or Sudan Black, combined esterase). Can be omitted if 4 colour flow cytometry is available.
4. Cytogenetics (with reverse transcription-polymerase chain reaction [RT-PCR] for AML1-ETO and CBFB-MYH11 in non-acute promyelocytic leukemia (APL) and PML-RARA in suspected APL; fluorescent in situ hybridization [FISH] in selected cases).

Treatment of Acute Myeloid Leukemia (AML)

General Measures and Supportive Care

Prevention of Tumour Lysis Syndrome

1. Rasburicase should be used with chemotherapy in patients with a white cell count $>100 \times 10^9/L$ at risk of acute tumour lysis syndrome (**Recommendation Grade B; Evidence level IIb**)

Bacterial Infection

1. There is no firm evidence of a survival advantage to support the routine use of prophylactic antibiotics in patients with AML and they are currently not recommended. Further large controlled trials are warranted. (**Recommendation grade B; evidence level IIb**)

Growth Factors

1. There is no survival benefit from the use of growth factors following AML chemotherapy but growth factor use does reduce the duration of neutropenia, of antibiotic use and of hospital stay. The cost benefit advantages of routine growth factor use are uncertain. The routine use of growth factor therapy in AML is not recommended. (**Recommendation Grade A; Evidence level IIa**)

Treatment of Younger Adult Patients

1. All eligible patients up to age 60 (or greater than 60 but able to receive intensive treatment) with de novo or secondary AML should be asked to participate in the current UK National Cancer Research Institute (NCRI) study, at present AML 15 (www.aml15.bham.ac.uk/trial/index.htm).
2. Patients over 60 able to tolerate remission induction chemotherapy should be asked to participate in the current NCRI study, at present Leukemia Research Foundation (LRF) AML 14 (<http://www.aml14.bham.ac.uk>) or HOVON/SAKK AML43.
3. Patients not eligible or unwilling to participate in the NCRI studies should be offered standard daunorubicin and cytarabine 3+10 or 3+7 induction chemotherapy (**Level 1b**)

4. Patients opting for non-intensive chemotherapy who are not entered into clinical trials should be offered treatment with low-dose cytarabine (**Recommendation grade A; Evidence level Ib**). Patients not able to tolerate chemotherapy should be given best supportive care: transfusion support and hydroxycarbamide to control the white count (**Recommendation grade A; Evidence level Ib**).

Management of AML in Patients who are Pregnant

1. AML in pregnancy should be managed jointly between the haematologist and the obstetrician with full involvement of the mother. (**Recommendation grade B; Evidence level III**)
2. Chemotherapy in the first trimester is associated with a high risk of fetal malformation and should be avoided if possible. The opportunity to terminate the pregnancy should be discussed with the mother. If termination is refused and the mother's life is at risk, chemotherapy should be started. (**Recommendation grade B; Evidence level III**).
3. Chemotherapy in the second and third trimesters is associated with an increased risk of abortion and premature delivery as well as small-for-dates babies. Consideration should be given to early induced labour between cycles of chemotherapy. (**Recommendation grade B; Evidence level III**).
4. All trans retinoic acid (ATRA) can be used in pregnancy in the second and third trimesters (**Recommendation grade B; Evidence level III**).

Management of Extra-Medullary Disease

1. Patients presenting with extramedullary leukaemia should receive systemic antileukaemic chemotherapy. (**Recommendation grade C; Evidence level IV**).

Acute Promyelocytic Leukemia (APL)

1. ATRA should be started as soon as the diagnosis is suspected (**Recommendation grade A; Evidence level Ib**).
2. Leucopheresis should be avoided in high count patients. (**Recommendation grade B; Evidence level III**).
3. The coagulopathy should be treated to keep the platelets $>50 \times 10^9/L$, together with fresh frozen plasma (FFP) and cryoprecipitate to normalise the activated partial thromboplastin time and fibrinogen levels (**Recommendation grade B; Evidence level IIb**).
4. ATRA syndrome should be treated promptly with dexamethasone 10mg twice daily intravenously, until the symptoms resolve. (**Recommendation grade C; Evidence level IV**).
5. Diagnostic work-up should include documentation of underlying PML-RARA fusion. (**Recommendation grade B; Evidence level IIa**).
6. Patients with PML-RARA positive APL, deemed suitable for intensive therapy, should be treated with concurrent ATRA and anthracycline-based chemotherapy for induction, followed by anthracycline-based consolidation therapy and should be offered entry into the NCRI AML trial (currently AML15) (**Recommendation grade A; Evidence level Ib**).
7. Patients should undergo molecular monitoring after treatment to guide further therapy. (**Recommendation grade B; Evidence level IIa**)

8. For relapsed disease, ATRA should not be used as single agent therapy due to significant possibility of acquired secondary resistance and arsenic trioxide (ATO) should only be used in patients with confirmed PML-RARA positive APL (**Recommendation grade B; Evidence level IIa**).

Transplantation in AML

1. Patients should be fully informed of both the advantages and disadvantages of the available treatments, and of the strategies that can be used to treat long-term side effects, particularly in the area of sexual function and infertility.
2. Intensive consolidation chemotherapy treatment during first complete remission (CR) should be offered as the preferred treatment to patients with favourable cytogenetics and to those unwilling to accept the risk of permanent damage to their sexual health and fertility, with bone marrow transplantation (BMT) remaining as the choice for salvage treatment in the event of relapse.
3. All patients of childbearing years undergoing BMT should be offered the opportunity of preserving their fertility (where possible) prior to treatment.
4. Allogeneic transplantation should be offered to patients with high risk AML (risk groups are defined in Table 2 of the original guideline document) in first remission who have an HLA identical donor, although it is accepted that only a minority of patients will benefit. (**Recommendation grade B; Evidence level III**). Standard risk patients may be offered allo-transplantation as part of a clinical trial (**Recommendation grade B; Evidence level III**).
5. Allogeneic transplantation may be the treatment of choice for younger patients who are in second remission. (**Recommendation grade B; Evidence level III**).
6. Older patients with high-risk disease or beyond first remission may be offered a reduced intensity transplant but this should be in the context of a clinical trial. (**Recommendation grade C; Evidence level IV**).
7. Younger high-risk patients or those beyond first remission may be considered for a haploidentical transplant but this should be in the context of a clinical trial. (**Recommendation grade C; Evidence level IV**).
8. The role of autografting in the management of AML is contentious. Autografting should only be carried out in a clinical trial. (**Recommendation grade A; Evidence level Ib**).

Acute Myeloid Leukemia in the Elderly

1. For patients in whom intensive chemotherapy is deemed justified (e.g. age <70 years, good performance status, white blood cell (WBC) <100 x 10⁹/L, no adverse cytogenetic abnormalities or multidrug resistance (MDR) expression), standard induction chemotherapy with daunorubicin (or an equivalent anthracycline) for 3 days plus cytarabine for 7-10 days is recommended (**Recommendation grade A, Evidence level Ib**). Where possible patients should be entered into clinical trials.
2. There is no firm evidence to date to support the use of MDR-blocking agents as an adjunct to induction chemotherapy (**Recommendation grade A recommendation; Evidence level Ib**).
3. Similarly there is insufficient evidence to support routine use of G-colony stimulating factor (CSF) or granulocyte macrophage (GM)-CSF with induction

- chemotherapy in patients over 60 years of age, although this may be appropriate if it is desirable to reduce hospitalisation or antibiotic usage (**Recommendation grade A, Evidence level Ib**).
4. The optimal post-remission chemotherapy for older adult patients with AML remains unclear. There does not seem to be a role for extended consolidation chemotherapy or maintenance treatment (**Recommendation grade A, Evidence level Ib**).
 5. Gemtuzumab ozogamicin shows promise as a salvage agent in patients with relapsed disease, and may be preferable to further intensive chemotherapy in this setting (**Recommendation grade B, Evidence level IIb**).

Non-intensive Palliative Chemotherapy

1. Unless patients opting for palliative chemotherapy are entered into clinical trials, treatment should be offered with low-dose cytarabine (**Recommendation grade A; Evidence level Ib**).

Definitions:

Classification of Evidence Levels

Ia Evidence obtained from meta-analysis of randomized controlled trials.

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CLINICAL ALGORITHM(S)

None provided

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 acute myeloid leukaemia (AML), including control of disease, prevention of complications, improved quality of life, and prolonged survival

POTENTIAL HARMS

Side effects of treatment, adverse events, treatment-related mortality

CONTRAINDICATIONS

CONTRAINDICATIONS

Tranexamic acid may be useful for local bleeding (e.g. oral haemorrhage) but its use is contraindicated in the presence of haematuria because of the possibility of ureteric clot formation.

QUALIFYING STATEMENTS

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While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, neither the authors, the British Society for Haematology nor the publishers accept any legal responsibility for the content of these guidelines.

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

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Milligan DW, Grimwade D, Cullis JO, Bond L, Swirsky D, Craddock C, Kell J, Homewood J, Campbell K, McGinley S, Wheatley K, Jackson G. Guidelines on the management of acute myeloid leukaemia in adults. London (UK): British Society of Haematology (BSH); 2005 May 23. 77 p. [202 references]

ADAPTATION

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

DATE RELEASED

2005 May 23

GUIDELINE DEVELOPER(S)

British Committee for Standards in Haematology - Professional Association

SOURCE(S) OF FUNDING

British Committee for Standards in Haematology

GUIDELINE COMMITTEE

Not stated

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Authors: Milligan DW; Grimwade D; Cullis J O; Bond L; Swirsky D; Craddock C; Kell J; Homewood J; Campbell K; McGinley S; Wheatley K; G Jackson

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 N19PF; E-mail: jules@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 26, 2006. The information was verified by the guideline developer on October 25, 2006. This summary was updated by ECRI Institute on February 26, 2008 following the U.S. Food and Drug Administration advisory/voluntary market withdrawal of the liquid formulation of Leukine (sargramostim).

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