



Clinical Guidelines for Leukaemia and other Myeloid Disorders – AML

Reference Number	Version	Status	Executive Lead(s) Name and Job Title	Author(s) Name and Job Title
13-2H-106	5		Dr Helen Barker MDT Lead Clinician	Dr H Kaur
Approval Body		SY Region Haematology MDT		Date Approved 19/07/2019
Ratified by		The Sheffield Teaching Hospitals NHS Foundation Trust (STHFT), Barnsley Hospital NHS Foundation Trust (BHNFT), Chesterfield Royal Hospital NHS Foundation Trust (CRHFT), Doncaster and Bassetlaw Hospitals NHS Foundation Trust (DBHNFT) and The Rotherham NHS Foundation Trust (TRFT)		Date Ratified 19/07/2019
Date Issued				Review Date July 2020
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Version History

Version	Date Issued	Brief Summary of amendments	Owner's Name:
1			Dr H Kaur
2	24/05/16	Diagnostic guidelines updated Diagnosis and treatment of AML updated	Dr H Kaur
3	26/04/17	Tumour lysis syndrome updated	Dr H Kaur
4	25/05/18	Diagnostic guidelines updated Diagnosis and treatment – molecular studies updated, Tumour lysis syndrome updated, bacterial infections updated, Fungal infection updated, growth factors updated Treatment of acute myeloid leukaemia in Younger Patients updated Transplantation in AML updated Acute Promyelocytic Leukaemia (APL) updated Management of APL patients at high risk of relapse updated Acute Myeloid Leukaemia in the Older Patient updated	
5	19/07/19	Addition of WGS to diagnosis section	Dr H Barker

(Please note that if there is insufficient space on this page to show all versions, it is only necessary to show the previous 2 versions)

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SECTION 1: DIAGNOSTIC GUIDELINES FOR ACUTE MYELOID LEUKAEMIA

All patients with suspected or known acute myeloid leukaemia should be referred to a haemato-oncologist for evaluation with minimum delay. Patients with a confirmed diagnosis should be discussed at the network multi-disciplinary meeting (MDM) for management review and treatment recommendation. As per NICE guidance, the multidisciplinary team serves a population of >500,000. As per the updated Improving Outcomes Guidance for Haematology, intensive induction chemotherapy should only be carried out in centres treating at least 10 patients per year with induction chemotherapy with curative intent. Patients ≤ 25 years should also be discussed at the Teenage and Young Adult (TYA) MDM

This will usually mean that patients are discussed at:

1. Initial presentation
2. After completion of induction chemotherapy
3. At relapse/ in the event of disease refractoriness*
4. If haematopoietic stem cell transplant is being considered

Patient co-morbidity data and performance status should be included with patient's clinical information for MDM discussion:

<http://biomedcentral.com/content/supplementary/1471-2407-4-94-S1.xls>

The MDM acknowledges that it may be necessary for clinicians to commence induction chemotherapy ahead of a MDM review where it is in the patients' best interests.

Diagnostic investigation

Peripheral blood film, bone marrow aspirate, bone marrow; cytogenetics, flow cytometry and molecular genetics are the diagnostic tissue samples of choice. **All diagnostic tissue samples should be sent to the Haemato-Oncology Diagnostic Service (HODS) with minimum delay.** In patients who are too frail to have a bone marrow aspirate due to advanced age (age more than 80 years) or poor performance status (ECOG >2) should still have their peripheral blood film, and peripheral blood EDTA sample for immunophenotyping +/- peripheral blood for karyotyping sent to HODS for definitive diagnosis.

SECTION 2: DIAGNOSIS AND TREATMENT OF AML

Introduction

National guidelines for the management of AML were published by the British Committee for Standards in Haematology (Milligan et al 2006) with newer Guidelines specifically tailored for the diagnosis and Management of AML in pregnancy (Ali et al 2015). The North Trent guidelines for the diagnosis and treatment of AML are based on these documents.

The newly diagnosed patient, and those with relapsed disease should have the diagnosis of AML and its treatment options explained to them in a manner that they can understand. Ideally, written information should also be provided to the patient, and their family. All patients should also be offered a copy of the letter outlining the discussion of diagnosis and treatment with their haematologist, introduced to their Key Worker/ Haematology Clinical Nurse Specialist, undergo a holistic needs assessment, and be given information for contacting the department during working hours and out-of-hours. A GP cancer diagnosis notification fax of should be sent within 24-hours of the patient being notified of their diagnosis.

http://www.cquins.nhs.uk/download.php?d=resources/measures/Haematology_April2013.pdf

Although a clinician may need to commence treatment prior to discussion at the Regional Haem-Onc MDM, the patient should be presented to the MDM at the earliest opportunity thereafter do that a treatment recommendation can be made by the MDM.

Diagnostic samples

Written consent should be obtained from all patients for bone marrow samples. **Patients should be asked whether they give consent for samples to be used for research purposes for potential entry, to avoid unnecessary repeat bone marrow sampling.**

1. Morphology

Unstained *bone marrow aspirate slides [minimum of 6] to allow:

- Quick stain
- 2 MGG
- Iron stain
- Two unstained peripheral blood films

*Provided that a particulate/cellular aspirate sample is obtained, aA trephine biopsy is desirable in all patients at diagnosis. Trephine biopsies for follow-up samples may not be required unless the diagnostic sample had significant fibrosis (European Consensus Grade 2 or 3) or if the aspirate sample appears haemodilute/ suboptimal.

2. Immunophenotyping

Bone marrow aspirate in EDTA for immunophenotyping (<24 hours old); peripheral blood may be sent if a high blast count is noted in peripheral blood.

3. Cytogenetics

Bone marrow aspirate in HAMS fluid. Peripheral blood may be sent for cytogenetics in Lithium Heparin if high peripheral blast count ($>1.0 \times 10^9/L$) is noted.

4. Molecular Haematology

Bone marrow aspirate in EDTA.

Patients of any age being considered for chemotherapy should have samples sent for molecular profiling for at least FLT3 and NPM1 mutation status. Additional molecular mutation profiling by high throughput or Next Generation Sequencing (NGS) is also advisable, especially since targeted therapies are becoming more commonplace, particularly in the clinical trial setting and may Patients who may be eligible for clinical trials should also have additional trial samples taken.

5. Other initial investigations

- Full blood count and film
- Clotting screen (including D-dimer in suspected APLM)

- Haematinics (B12/ folate/ ferritin)
- U&E and Liver function tests
- Bone profile/ uric acid, LDH
-
- Blood group and save
- Pregnancy test (women of childbearing potential)

- Viral screen (HIV, Hep B, Hep C)
- n.b. HIV Ag/Ab, HBsAg, HBc total Ab, HCV Ab, HTLV1/2 Ab testing is required for those patients requiring fertility cryopreservation
- PNH screen (cytopenia of uncertain cause)

6. Additional tests for patients likely to receive intensive chemotherapy

- Hep E screen
- HLA Class I & II typing
- CMV IgG

7. Whole Genome Sequencing (WGS)

In addition to the standard of care tests described above currently the following patients are eligible for WGS

- All patients (adults and paediatric) with acute myeloid leukaemia (AML)
- All patients (adult and paediatric) with acute leukaemia of ambiguous lineage

The samples can be at diagnosis or at relapse for each of the above. Bone marrow or peripheral blood with >20% blasts (any blast % if AML defining genetic abnormality is present) collected in EDTA. When a patient is confirmed with a diagnosis of AML the treating clinician will be informed and requested to send patient consent including record of discussion and to obtain a germline sample. The part of the WGS order form pertaining to the germline sample should be completed by the clinician/SpR or Clinical Nurse Specialist taking the germline sample. For germline DNA samples the following are considered:

- Saliva post treatment (following 2 courses of anthracycline chemo in AML or post confirmation of no blasts by morphology for ALL)
- Cultured fibroblasts from a skin puncture biopsy , the sample of choice
- Uncultured skin puncture biopsy

Send germline samples to Sheffield HODS laboratory for onward dispatch to SDGS at SCH.

Hyperleucocytosis

Hyperleucocytosis is defined by a white count of more than $100 \times 10^9/L$ at the time of presentation, and has been identified as an adverse prognostic marker in some series, predicting for early death (Powles 2003).

There are no randomised controlled trials that support the regular use of leucopheresis in the management of leucostasis, and it is contraindicated in patients with APL. However, it should be considered in patients who present with high white count and symptoms attributable to leucostasis (e.g. hypoxia, confusion). Alternatively, hydroxycarbamide may be used in large doses (e.g. 2-3g po tds) to reduce the peripheral count over 24-36 hours.

Tumour Lysis syndrome

Patients at highest risk of developing tumour lysis syndrome on commencement of remission induction therapy include those with:

1. Acute myelomonocytic or monoblastic leukaemia ($WBC > 150 \times 10^9/L$)

Patients at high risk of developing tumour lysis syndrome (TLS) should receive the following

- Hydration (3L/24hr) to achieve urine output $> 100 \text{ mL/hr}$.
- Rasburicase should be used in preference to allopurinol in patients at very high risk of tumour lysis. Patients with known G6PD deficiency may have adverse reaction to rasburicase, and require the following alternative regimen for treatment of TLS:
 - Allopurinol $100 \text{ mg/m}^2/\text{dose}$ q8 h po (maximum 800 mg/day) or $200\text{-}400 \text{ mg/m}^2/\text{day}$ in 1-3 divided doses i.v. (maximum 600 mg/day). Reduce dose by 50% or more in renal failure. Doses of drugs metabolised by the P₄₅₀ hepatic microsomal enzymes with concomitant allopurinol
 - The use of sodium bicarbonate to alkalinize the urine is not recommended in the ward-based setting. The maximal solubility of urate occurs at a pH of 7.5 and at alkaline urine pH (≥ 6.5) the solubility of xanthine and hypoxanthine significantly decreases, leading to the development of urinary xanthine crystals during and after allopurinol therapy. Overzealous systemic and urinary alkalinisation may lead to metabolic alkalosis and/or xanthine obstructive uropathies.

Allopurinol 300mg daily should be used as standard TLS prophylaxis in all patients. Doses may need to be modified in the presence of renal impairment.

- Laboratory monitoring (K, Ca, urea, creatinine, LDH, uric acid) bd for 24-48 hours
- If baseline creatinine elevated consider urinary catheter, US kidneys and Renal consult (Urology consult if obstruction)

Red cell transfusion support

1. Patients treated with fludarabine/ cladribine/ purine analogue-based chemotherapeutic regimens should be supported with irradiated blood products
2. Iron overload may occur. It may be important to assess iron load in patients who have completed therapy and some patients in remission with iron overload may benefit from venesection.

3. Where possible chlorpheniramine should be used to control allergic reactions, and additional hydrocortisone where required.

Platelet support

1. A threshold of $10 \times 10^9/L$ is as safe as higher levels for patients without additional risk factors.
2. The platelet count should be kept at $>20 \times 10^9/L$ in patients who are haemorrhagic or septic, or greater than $50 \times 10^9/L$ in patients with acute promyelocytic leukaemia who are bleeding
3. 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.
4. Platelet refractoriness due to shortened platelet survival associated with non-immune clinical factors, such as infection (including its treatment with antibiotics and antifungal drugs), DIC and splenomegaly. However, all patients in whom remission induction chemotherapy is planned should have HLA Class I & II tissue type before therapy is started.

Antibiotic and Antimicrobial therapy

- Patients should pay careful attention and instruction in, personal hygiene and dental care for the duration of their treatment.
- Hand washing and decontamination before contact with the patient is mandatory for all health care workers and visitors.
- Patients requiring indwelling catheters (e.g. Hickman or PICC lines) require decolonisation as per local policy with Chlorhexidine 4% or Octenisan washes, in addition to nasal prontosol topically tds for a total of 5 days starting 2 days before the scheduled line insertion.
- Flowers and pot plants are a potential source of fungal spores and pseudomonas and should be removed from the unit. Each unit should have a policy on the microbiological safety of food and water.
- The patient should be examined regularly and carefully including examination of the mouth and throat
- Vaginal and rectal examination should only be performed if absolutely necessary on clinical grounds.
- Chest X-rays should be performed regularly, if the patient is unwell, and high resolution CT scans of the chest should be considered to exclude pulmonary aspergillosis and other infections. X-rays or computerised tomography of the sinuses may also be helpful to exclude occult fungal infections.

Bacterial infection

- Patients should be made aware of their susceptibility to infection and of the importance of presenting early to hospital, appropriate contact numbers should be given.
- NICE Guidelines published in 2012 recommend the use of fluoroquinolone prophylaxis in adults aged 18 or older with acute leukaemias or undergoing haematopoietic stem cell transplantation with expected significant neutropenia (neutrophils $\leq 0.5 \times 10^9/L$) for the expected duration of neutropenia only

- Rates of antibiotic resistance and infection patterns should be monitored in treatment facilities where patients are having fluoroquinolones for the prophylaxis of neutropenic sepsis.
- Refer to local guidelines for the management of patients admitted as an emergency with neutropenic sepsis including antibiotic protocol. The antibiotic protocol reflects bacterial resistance patterns within the haematology unit and hospital, and has been decided in conjunction with the local microbiology department and NICE Guidance for the management of patients with suspected neutropenic sepsis (Neutropenic sepsis: prevention and management in people with cancer. Clinical Guideline CG151: September 2012. <https://www.nice.org.uk/guidance/cg151>)

Fungal infection

There should be a written local guideline for early empiric anti-fungal therapy in neutropenic patients with refractory fever. Haematologist should have rapid access to high-resolution CT imaging, and bronchoscopy in order to facilitate diagnosis.

Growth Factors

NICE Guidelines do not recommend routine use of [G-CSF](#) for the prevention of neutropenic sepsis in adults receiving chemotherapy unless they are receiving G-CSF as an integral part of the chemotherapy regimen or in order to maintain dose intensity. G-CSF may be considered only in the setting of acute myeloid leukaemia during induction chemotherapy in patients with overwhelming sepsis, as G-CSF can influence bone marrow appearances and render interpretation of repeat bone marrow samples difficult. G-CSF may be given to patients with acute myeloid leukaemia who are known to be in complete morphological and cytogenetic/ molecular remission post-induction chemotherapy

Treatment of acute myeloid leukaemia in Younger Patients

All eligible patients up to age 60 years (or greater than 60 but able to receive intensive treatment) with de novo or secondary AML should be asked to participate in the current NCRI study, at present AML19.

OFF TRIAL (non APL)

Induction therapy

- Daunorubicin and Cytarabine (3+10) regimen.
- Midostaurin is recommended, within its marketing authorisation, as an option in adults for treating newly diagnosed acute FLT3-mutation-positive myeloid leukaemia with standard daunorubicin and cytarabine as induction therapy, with high-dose cytarabine as consolidation therapy, and alone after complete response as maintenance therapy.

<https://www.nice.org.uk/guidance/gid-ta10124/documents/html-content-2>

Midostaurin will be available via the cancer Drugs fund (CDF) from 04 May 2018 in line with these recommendation and according to a set of treatment criteria which translates the NICE recommendation into a clinical guide to use in practice.

<https://www.england.nhs.uk/cancer/cdf/cancer-drugs-fund-list/>

NHSE will then routinely commission midostaurin as an option for treating adults with newly diagnosed acute FLT3-mutation-positive AML 90 days after the day of publication of the final guidance.

- Patients who do not achieve at least a partial remission, preferably <15% blasts after remission induction treatment should be considered for treatment on a 'high-risk' trial

protocol if available. Otherwise FLAG-Ida, or high-dose/ mega-dose Cytarabine or G-CLAC as bridge to transplantation (see National CDF list) may be considered as possible salvage regimens.

- Patients aged between 60-75 years with secondary AML (therapy-related AML, or AML secondary to MDS or CMML, or high risk MDS karyotype) are currently eligible for CPX-351 or Vyxeos on a named patient, compassionate use basis directly from the pharmaceutical company.

Post remission therapy

The aim of post remission consolidation therapy is to reduce relapse risk. Therapeutic strategies include consolidation chemotherapy, allogeneic transplantation, or high-dose therapy and autologous stem cell transplant. Consolidation treatment should reflect the patients disease risk group, stem cell donor availability and patient eligibility for transplant.

a. *Favourable risk AML*

Patients with favourable karyotype who have achieved remission with induction therapy should receive consolidation chemotherapy. Although standard and high-dose cytarabine based regimens have been used, the optimal consolidation regimen is unknown. Patients not enrolled on a NCRI trial should be considered for either:

MRC AML17-based post-remission therapy:

Course 2

DA 3+8 : Daunorubicin given for 3 days at a dose of 50mg/m² and Cytarabine 100mg/m² twice for 8 days

Course 3 & 4:

HD AraC : Cytarabine 3g/m² IV 12 hourly on days 1, 3 and 5 for patients <60 years

Or

HD AraC : Cytarabine 1.5g/m² IV 12 hourly on days 1, 3 and 5 for patients >60 years

b. ****Standard and Poor risk AML (Off-Trial)**

Patients with standard risk AML aged 40-60 years should be considered for allogeneic transplant in first remission if they have a suitable matched sibling donor.

Matched unrelated allogeneic transplant in first complete remission should be considered in patients with **poor risk disease**.

- Patients in 1st complete remission (CR1) with adverse risk cytogenetics
- Patients who failed to achieve morphological remission after the first course of induction therapy
- Patients with FLT-3 ITD positive AML
- Patients with persistent or rising MRD levels (by immunophenotypic or molecular monitoring) who have a morphological CR
- Patients who have been defined as high risk in the UK NCRI clinical trials
- Patients with secondary AML
- Patients >60 years deemed fit for intensive treatment options

All patients where allogeneic transplantation is being considered should be referred to the Transplant team at STH in a timely manner to allow appropriate counselling and work-up.

(BCSH Guidelines 2015: Management of AML in pregnancy)

1. AML in pregnancy should be managed jointly between the haematologist and the obstetrician with full involvement of the mother. (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. (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. (Grade B; evidence level III).
4. ATRA can be used in pregnancy in the second and third trimesters (Grade B; evidence level III).
5. Finally further information is required about the outcome of pregnant patients with cancer and new cases should, with the consent of the patient, be reported to the International Registry of Cancer in Pregnancy (<http://www.motherisk.org/cancer/index>).

Management of extra-medullary disease

Patients presenting with extramedullary leukaemia should receive systemic antileukaemic chemotherapy.

Management of central nervous system disease

Whenever possible suspected disease in the CSF should be confirmed by immunophenotyping, as cytospin morphology may be misleading when cells are scanty.

- In suspected CNS disease at presentation 50mg of cytarabine should be given intrathecally at the time of the diagnostic lumbar puncture.
- If infiltration is confirmed, intrathecal cytarabine 50mg should be given 2-3 times per week until the CSF is clear, and then fortnightly until consolidation treatment is completed.
- Depocyte may be considered to reduce frequency of treatment (weekly for 5 doses, then every 2 weeks for 5 doses with oral prednisolone cover), and improve quality of life.
- Re-induction chemotherapy should be given in addition to intrathecal treatment, and inclusion of high dose cytarabine may be helpful

Management of relapsed AML

Many patients who receive salvage therapy at the time of first relapse have unsatisfactory treatment outcomes and often short remission durations particularly if the duration of first remission is less than 6 months. Several prognostic factors influence outcome and include:

1. Duration of first remission
2. Patient age
3. Cytogenetics at the time of original presentation

The decision to treat the patient with relapsed disease should take into account prognostic factors. The HOVON prognostic index² can be used to define outcome risk and may aid decision making

Three prognostic sub-groups can be defined. Patients with prognostic scores of 10-14 should be considered for palliation or experimental therapy.

Group A:	Overall survival 70% at 1 year and 46% at 5 years	Score 1-6
Group B:	Overall survival 49% at 1 year and 18% at 5 years	Score 7-9
Group C	Overall survival of 16% at 1 year and 4% at 5 years	Score 10-14

Prognostic Factor	Points
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Relapse-free interval from first complete Remission, months

>18 months	0
7-18 months	3
≤ 6 months	5

Cytogenetics at diagnosis

t(16;16) or inv(16)*	0
t(8;21)*	3
Other†	5

Age at first relapse

≤ 35 years	0
36-45 years	1
> 45 years	2

Stem-cell transplantation before first relapse

No SCT	0
Previous SCT (allogeneic or autologous)	2

Although the optimal salvage regimen for patients with relapsed disease is unknown, most regimens rely upon high-dose cytarabine in combination with other chemotherapeutic agents e.g. FLAG-Ida, or as single agent. Patients deemed suitable for intensive salvage therapy should be referred to the North Trent Bone Marrow Transplant Programme to discuss the possible role of bone marrow/ stem cell transplantation in their salvage management.

Transplantation in AML

All patients in whom bone marrow transplant is being considered should be referred to the North Trent Bone Marrow Transplant Programme for appropriate counselling and planning. The following recommendations outline the groups of patients with AML who may benefit from allogeneic transplantation:

1. Allogeneic transplantation should be considered in first remission for patients with high-risk disease (not in morphological remission after induction #1, or with adverse cyto-and/ or molecular genetics). **Standard risk patients between 40-60 years may be offered an allogeneic transplant in first remission if they have a suitable sibling HLA matched donor
2. Young patients with relapsed disease in whom intensive salvage is being planned should be considered for allogeneic transplantation
3. Older patients (age 60 years and above), with high-risk disease, or with relapsed disease should be considered for reduced intensity allogeneic transplantation in the context of a clinical trial, if available, or after consideration on an individual case by case basis by the Network MDM.
4. Patients who are MRD positive after 1 cycle of remission induction chemotherapy + 1 further cycle of consolidation chemotherapy in morphological CR1

**Retrospective trial data (Gale et al 2008, Schlenk et al 2008) suggest that patients with normal karyotype who are *NPM1* mutation positive and *FLT3-ITD* negative, MRD negative and in CR1 have a relatively good prognosis. Patients with normal karyotype should undergo screening for molecular genetic mutations by NGS as part of the initial work up.

Intermediate and high risk patients without a matched related donor should be referred to the transplant centre at the earliest opportunity. These patients will be considered for matched unrelated donor transplant in first remission and may require consideration for haploidentical, cord or mismatched donor options if needed).

Acute Promyelocytic Leukaemia (APL)

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 NCRI study, at present AML19.

The following should be considered in APL:

1. ATRA should be commenced as soon as the diagnosis of APL is suspected. Under no circumstances should treatment be delayed until the diagnosis has been confirmed by cytogenetic or molecular analysis because of the risk of early death.
2. Continue ATRA until first CR is achieved or until completion of 2 courses of chemotherapy for a maximum of 60 continuous days
3. Leucopheresis should be avoided in high count patients. During induction platelet count should be maintained at $>50 \times 10^9/L$, together with fresh frozen plasma (FFP) and cryoprecipitate to normalise the activated partial thromboplastin time and fibrinogen levels Activated partial thromboplastin time (APTT), prothrombin time (PT), thrombin time (TT), fibrinogen level and platelet count should be checked at least twice daily during the early stages of treatment.
4. Diagnostic work-up should include documentation of underlying PML-RARA fusion.

5. Patients with PML-RARA positive APL, deemed suitable for intensive therapy treated off trial should receive
 - a. Arsenic chemotherapy: NICE in the final appraisal determination on 4th May 2018 stated that arsenic trioxide is recommended as an option for inducing remission and consolidation in acute promyelocytic leukaemia in adults with
 - Untreated, low-to-intermediate risk (defined as WCC of $\leq 10 \times 10^3/\mu\text{L}$) when given with all-trans-retinoic acid (ATRA)

<https://www.nice.org.uk/guidance/gid-ta10216/documents/final-appraisal-determination-document>

Arsenic trioxide will be available via the Cancer Drugs fund (CDF) from 04 May 2018 in line with these recommendations and according to a set of treatment criteria which translates the NICE recommendation into a clinical guide to use in practice.

<https://www.england.nhs.uk/cancer/cdf/cancer-drugs-fund-list/>

NHSE will then routinely commission arsenic in patients with APL, incorporating these treatment criteria, from 90 days after the day of publication of the final guidance.

Dosing and schedule of administration for arsenic trioxide must be either in accordance with that described in the SPC or that used in the UK NCRI AML17 trial as reported in Lancet Oncology 2015; 16:1295-1305. If the AML17 dosing and schedule is used, hospital Trust policy regarding unlicensed treatments should be followed.
 - b. AIDA chemotherapy: concurrent ATRA and anthracycline-based induction, followed by 3 cycles of AIDA (anthracycline-based) consolidation therapy
6. Patients should undergo molecular minimal residual disease (MRD) monitoring with a repeat bone marrow aspirate (5ml in EDTA) + peripheral blood (20ml in EDTA) after every cycle of chemotherapy, and every three months after completion of chemotherapy for a duration of 2 years.

ATRA syndrome

- ATRA should be temporarily discontinued and steroids administered promptly (dexamethasone 10mg iv bd until disappearance of symptoms and signs, and for a minimum of 3 days)
- Because RA syndrome is linked to differentiation of APL blasts, its occurrence during induction is not a contraindication to use of ATRA later in the patient's treatment course (including management of any relapse).
- Patients with a relatively high presenting WBC ($>10 \times 10^9/\text{L}$) have in some studies been reported to be at higher risk of RA syndrome during induction and some trial groups advocate use of prophylactic steroids (dexamethasone 10mg po bd) as a component of induction therapy.

Management of APL patients at high risk of relapse

Patients with persistent disease or molecular relapse, confirmed on 2 consecutive assays after completion of consolidation.

- Arsenic trioxide (ATO) as single agent following failed treatment with AIDA or anthracycline based chemotherapy
(Patients who relapsed or failed to achieve MRD negative remission having received ATO as first line therapy should not receive ATO again; they should receive AIDA or anthracycline based chemotherapy +/- Gemtuzumab on compassionate use basis)
- Gemtuzumab on compassionate use basis either as single agent or in conjunction with chemotherapy
- Once PCR negativity has been achieved, stem cells may be harvested and if confirmed to be PCR negative, autologous stem cell transplantation (SCT) can be undertaken
- Allogeneic-BMT may be curative, and should be considered in patients with a matched donor.

Management of APL relapse

1. Arsenic trioxide (ATO)/ATRA should be considered in relapsed APL patients who received conventional ATRA anthracycline combination therapy as first line. ATO may induce a differentiation syndrome akin to ATRA syndrome, and if suspected it should be managed in the same way with prompt initiation of steroids and cessation of ATO.
2. ATRA combined with chemotherapy may be used to induce a second CR, but ATRA as single agent therapy should not be relied upon for treatment of relapse due to high rates of secondary resistance.
3. Gemtuzumab ozogomicin should be considered in those patients who fail to achieve molecular remission with ATO or ATRA/chemotherapy.

Acute Myeloid Leukaemia in the Older Patient

Acute myeloid leukaemia occurring in older adults (age 60 years or more) has a poor outcome to therapy, due to patient and disease related factors. The decision to elect for either 'curative' or palliative therapy is key in this patient group.

Intensive chemotherapy

Patients with *de novo* AML with standard or favourable risk karyotype, and good performance status (ECOG 0-2) without significant comorbidities should be considered for 'curative' therapy with intensive chemotherapy. However, the optimal induction, and consolidation regimens are unknown

Patients in whom intensive chemotherapy is deemed appropriate should be asked to participate in the current NCRI study, at present **AML 18**

OFF TRIAL

Patients receiving intensive chemotherapy off trial should receive Daunorubicin + Cytarabine 3+10 induction chemotherapy, followed by consolidation chemotherapy. Patients with high risk disease

Patients aged between 60-75 years with secondary AML (therapy-related AML, or AML secondary to MDS or CMML, or high risk MDS karyotype) are currently eligible for CPX-351 or Vyxeos on a named patient, compassionate use basis directly from the pharmaceutical company.

Palliative therapy

Patients in whom non-intensive chemotherapy or supportive care only is deemed appropriate should be referred to their local specialist palliative care team at an early stage so that appropriate symptom control, and psychological support for the patient and family can be provided.

If palliative chemotherapy is appropriate patients should be asked to participate in the current NCRI study. If there is a clinical trial option for non-intensive treatments, this should be offered to eligible patients. If clinical trial options are inappropriate, then the following chemotherapeutic agents should be considered

- Hydroxycarbamide
- Low dose subcutaneous Cytarabine
- 5-Azacytidine (bone marrow blasts 20-30%)
- Clinical trials where available