ACUTE MYELOGENOUS LEUKEMIA AND ACUTE PROMYELOCYTIC LEUKEMIA
Union for International Cancer Control
2014 Review of Cancer Medicines on the WHO List of Essential Medicines

ACUTE MYELOGENOUS LEUKEMIA
(Including Acute Promyelocytic Leukemia)

Executive Summary

Acute myelogenous leukemia or acute myeloid leukemia (AML) is a heterogenous hematological malignancy involving the clonal expansion of myeloid blasts in the bone marrow and peripheral blood with possible spread to liver and spleen. An estimated 18,860 people were diagnosed in USA in 2014, 10,460 of whom will die from their disease. The median age at diagnosis is 66 years, with 54% patients over 65 years, and 33% over 75 years (1). Of those diagnosed at a later age, the diagnosis is often associated with underlying myelodysplastic syndromes (MDS), sometimes linked to cancer chemotherapy and radiotherapy exposure.

Public Health Relevance

GLOBOCAN estimates the worldwide total leukemia incidence of AML for 2012 to be 351,965 with an age-standardized rate (ASR) per 100,000 of 4.7, a 5-year prevalence of 1.5% and a M:F ratio of ~1.4 (2). In countries with “medium human development” the 2012 incidence was 136,378 with ASR per 100,000 of 3.8, while in countries of “low human development the incidence was 26,004 with ASR per 100,000 of 2.5. Mortality was 265,461 worldwide with ASR 3.4 per 100,000, with a mortality of 113,783 and ASR per 100,000 of 3.2 in countries with “medium human development” and 23,865 and ASR per 100,000 of 2.4 in countries of “low human development”. Unfortunately International Agency for Research on Cancer (IARC) does not sub-classify leukemias into acute and chronic, and myeloid or lymphoid in its GLOBOCAN analysis.

Classification

Two systems have been used to classify AML – the earlier French-American-British (FAB) classification and the more recent World Health Organization (WHO) classification.

The French-American-British (FAB) classification

In the 1970-80s, French, American, and British leukemia experts divided AML into 8 subtypes, based on the type of cell from which the leukemia developed and how mature the cells were:

<table>
<thead>
<tr>
<th>FAB subtype</th>
<th>Name</th>
</tr>
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<tbody>
<tr>
<td>M0</td>
<td>Undifferentiated AML</td>
</tr>
</tbody>
</table>
### World Health Organization (WHO) classification

In 2001, WHO classified AML based on prognostic factors affecting patients’ outlook:

1. **AML with genetic abnormalities:**
   - AML (M2) with t(8;21) translocation
   - AML (M4eos) with a translocation or inversion of chromosome 16 (AMML Eos)
   - AML with chromosome 11 abnormalities (Secondary AML)
   - AML (M3) with t(15;17) or rarely t(11;17) translocation (APML)

2. **AML with multilineage dysplasia:**
   - >1 abnormal myeloid cell type is involved

3. **Secondary AML:**
   - Related to previous chemotherapy or radiation exposure.

4. **AML not otherwise specified**
   - (AML that doesn’t fall into one of the above groups; similar to the FAB classification):
     - Undifferentiated AML (M0); AML with minimal maturation (M1); AML with maturation (M2); AMML (M4); AMoL (M5); Acute erythroid leukemia (M6); Acute megakaryoblastic leukemia (M7); Acute basophilic leukemia; Acute panmyelosis with fibrosis; Myeloid sarcoma.

5. **Undifferentiated or biphenotypic acute leukemias:**
   - Both lymphoid and myeloid features.
The WHO classification was revised in 2008 as follows:

**Acute myeloid leukemia and related neoplasms**
- Acute myeloid leukemia with recurrent genetic abnormalities
  - AML with t(8;21)(q22;q22); *RUNX1-RUNX1T1*
  - AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
  - APL with t(15;17)(q22;q12); *PML-RARA*
  - AML with t(6;11)(p22;q23); *MLLT3-MLL*
  - AML with t(6;9)(p23;q34); *DEK-NUP214*
  - AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*
  - AML (megakaryoblastic) with t(1;22)(p13;q13); *RBMY15-MKL1*
- Provisional entity: AML with mutated *NPM1*
- Provisional entity: AML with mutated *CEBPA*

**Acute myeloid leukemia with myelodysplasia-related changes**

**Therapy-related myeloid neoplasms**
- Acute myeloid leukemia, not otherwise specified
  - AML with minimal differentiation
  - AML without maturation
  - AML with maturation
  - Acute myelomonocytic leukemia
  - Acute monoblastic/monocytic leukemia
  - Acute erythroid leukemia
    - Pure erythroid leukemia
    - Erythroleukemia, erythroid/myeloid
  - Acute megakaryoblastic leukemia
  - Acute basoophilic leukemia
  - Acute panmyelosis with myelofibrosis

**Myeloid sarcoma**

**Myeloid proliferations related to Down syndrome**
- Transient abnormal myelopoiesis
- Myeloid leukemia associated with Down syndrome

**Blastic plasmacytoid dendritic cell neoplasm**
Prognostic Factors for AML

Cytogenetic and genetic factors: Chromosome and gene abnormalities:

**Favorable prognostic abnormalities:**
- t(8;21) (AML M2)
- Inversion of chromosome 16 or t(16;16) (AMML M4 eos)
- t(15;17) (APML M3)

**Intermediate prognostic abnormalities:**
- Normal karyotype

**Unfavorable prognostic abnormalities:**
- Deletion/loss of chromosome 5 or 7 – may be secondary to alkylating agent chemotherapy
- Translocation or inversion of chromosome 3
- t(6;9)
- t(9;22) - transformed CML or de novo AML or ALL
- Chromosome 11q23 abnormalities – secondary to topoisomerase inhibitor chemotherapy
- Monosomal karyotype involving a monosomy (loss of an entire chromosome) plus additional structural aberrations or more than a single monosomy
- Complex karyotype often involving ≥ 3 chromosomal abnormalities (no specific AML type)

**Note:** In patients with normal karyotype the following have prognostic implications:
- Mutation in the FLT3 gene results in a poorer outcome. 1 in 3 patients have an internal tandem duplication (ITD) mutation in the FLT3 gene which results in a poorer outcome, especially when both alleles are involved (resulting in a high FLT3-ITD/normal FLT3 ratio).
- Patients with mutations in the NPM1 gene (and no other abnormalities) have a better prognosis, as do patients with mutations in both alleles of the CEBPa gene (so called biallelic gene mutations).
Based on cytogenetics and the novel molecular parameters the following is the updated prognostic risk group stratification for AML:

### Clinical markers of prognosis:

**Age**
- Older patients (over 60) do not fare as well as younger patients as they are more likely to have unfavorable chromosome abnormalities as well as having comorbid medical conditions that can make it harder to use intense chemotherapy regimens. Older patients also suffer more from AML secondary to previous myelodysplastic syndrome which confers a worse prognosis.

**White blood cell count**
- A high white blood cell count (>100,000) at the time of diagnosis is linked to a worse outlook.

**Prior blood disorders or cancers**
- Preceding hematological disorders (e.g., polycythemia vera or marrow failure syndromes (Fanconi, congenital neutropenia and others) and myelodysplastic syndromes are linked to a poor outcome of AML.

### Table 1. European LeukemiaNet Standardized Reporting System for Correlation of Cytogenetic and Molecular Genetic Data in AML With Clinical Data

<table>
<thead>
<tr>
<th>Genetic Group</th>
<th>Subsets</th>
</tr>
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<tbody>
<tr>
<td>Favorable</td>
<td>t(8;21)(q22;q22); RUNX1-RUNX1T1</td>
</tr>
<tr>
<td></td>
<td>inv16(p13.1q22) or t(16;18)(p13.1;q22); CBFB-MYH11</td>
</tr>
<tr>
<td></td>
<td>Mutated NPM1 without FLT3-ITD (normal karyotype)</td>
</tr>
<tr>
<td></td>
<td>Mutated CEBPA (normal karyotype)</td>
</tr>
<tr>
<td>Intermediate-I</td>
<td>Mutated NPM1 and FLT3-ITD (normal karyotype)</td>
</tr>
<tr>
<td></td>
<td>Wild-type NPM1 and FLT3-ITD (normal karyotype)</td>
</tr>
<tr>
<td></td>
<td>Wild-type NPM1 without FLT3-ITD (normal karyotype)</td>
</tr>
<tr>
<td>Intermediate-II</td>
<td>t(8;11)(p22;q23); MLLT3-MLL</td>
</tr>
<tr>
<td></td>
<td>Cytogenetic abnormalities not classified as favorable or adverse</td>
</tr>
<tr>
<td>Adverse</td>
<td>inv(3)(q21q26.2) or t(3;3)(q21;q26.2); RPN1-EVI1</td>
</tr>
<tr>
<td></td>
<td>t(6;9)(p23;q34); DEK-NUP214</td>
</tr>
<tr>
<td></td>
<td>t(v;11)(vq23); MLL rearranged</td>
</tr>
<tr>
<td></td>
<td>−5 or del(5q)</td>
</tr>
<tr>
<td></td>
<td>−7</td>
</tr>
<tr>
<td></td>
<td>abl1(17p)</td>
</tr>
<tr>
<td></td>
<td>Complex karyotype*</td>
</tr>
</tbody>
</table>

*Abbreviations: AML, acute myeloid leukemia; ITD, internal tandem duplication. *Complex karyotype is defined as three or more chromosome abnormalities in the absence of one of the WHO designated recurring translocations or inversions: t(8;21), inv(16) or t(16;16), t(15;17), t(9;11), t(v;11)(vq23), t(6;9), inv(3) or t(3;3).
Treatment-related AML

- AML after previous chemotherapy or radiotherapy for another cancer or other disease (e.g. autoimmune disease) is linked to a worse outcome.

Requirements for diagnosis, treatment, and monitoring:

Diagnostics: AML requires laboratory access to come to a definitive diagnosis:

Peripheral blood:

- A phlebotomist, being a nurse, a doctor or a laboratory technician is required to draw peripheral blood and make smears in a patient presenting with one or more of anemia, abnormal bleeding and infection.
- A trained laboratory technician with access to a Coulter Counter is required to suspect the initial diagnosis by demonstrating a low/normal/high WBC with a low platelet count and an anemia.
- A trained hematologist is required to confirm the diagnosis by seeing “blast cells” in peripheral blood smear and plan a bone marrow aspirate and biopsy.

Bone marrow aspiration and biopsy:

- Bone marrow aspirates are part of the routine evaluation of AML. In scenario’s where there is a “dry tap” or absence of material in the aspirate, a bone marrow biopsy will also be required. Otherwise a biopsy is not required for standard evaluation and care. Smears (touch preps) of the biopsy should also be evaluated.
- This requires disposable or reusable biopsy needles and a doctor trained to perform bone marrow aspiration and biopsy.
- Laboratory facilities to stain the bone marrow samples and a trained hematopathologist are needed to morphologically evaluate the marrow specimens both at diagnosis and on follow-up.

Flow cytometry:

- A flow cytometry laboratory is needed to help sub-classify the AML and evaluate for prognostic factors.

Cytogenetic and molecular diagnostics:

- Conventional cytogenetics is required to demonstrate translocations, deletions, additions, monosomies and trisomies.
- FISH may substitute for only for specific cytogenetic abnormalities for which probes are available but it does not provide a complete karyotype. It is more sensitive but is implied when certain aberrations are suspected.
- RT-PCR is most sensitive assay to demonstrate translocations or certain molecular aberrations like FLT-3 and NPM1 and CEBPα.
- DNA sequencing is needed to demonstrate certain subtle mutations.
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Monitoring

Definitive diagnostic tests:
- CBC, INR/PTT, liver and kidney function tests, uric acid, bone marrow aspirate
- In certain cases, cytogenetics/FISH and PCR/sequencing may also be necessary

Supportive testing:
- Microbiology and biochemistry laboratory testing as well as radiology including plain X-rays (chest), CT scanning (brain, chest, abdomen/pelvis).

Follow-up testing:
- CBC and clotting parameters (daily), renal and liver functions (2 -7x/week), microbiology (as needed), radiology (as needed), bone marrow aspirate and biopsy (after every remission induction cycle and consolidation and thereafter every 6 months and on indication because of suspected or possible relapse), cytogenetic/molecular testing as needed.

Administration and Care of Patients:
Patients should be treated in reverse barrier nursed isolation facilities with adequate trained medical, nursing and pharmacy support. Central venous access and infusion pumps are needed for administration of chemotherapy as well as blood products, antibiotics and blood pressure support in case of ICU admission. ICU facilities needed to provide support in case of septic shock.

Supportive Care

Blood products:
- Red blood cells, preferable filtrated to remove contaminant white blood cells from the red blood cell concentrate, or irradiated
- Platelets: Pheresis (prefered) and pooled
- Fresh Frozen Plasma (FFP) – especially in APML
  Note: Blood product access may be limited by high incidence of HIV, HBV and HCV in certain countries.

Antibiotics:

Note: This section is to merely acknowledge that patients undergoing treatment for AML are at high risk for many infections, which are caused by a variety of organisms some of which can be resistant to multiple antibiotics. The availability of a wide spectrum of antibiotics can improve outcome for these patients. The follow serve only as some examples of infectious etiologies for these patients and antibiotics that can be used to treat them. Some of these antibiotics are not currently on the EML.

- Gram negative bacilli eg. Klebsiella, Pseudomonas:
  Sensitive: Piperacillin/tazobactam; cefipime; ceftazidime; ertapenem
ESBL: Meropenem; imipenem
CRE: Colimycin; tigecycline

- Gram positive cocci eg. Staphylococcus, Streptococcus
  
  **Sensitive**: Amoxicillin/clavulinate; cloxacillin
  
  **MRSA**: Vancomycin; linezolid

- Fungi eg. Candida, Aspergillus.
  
  **Candida**: Amphotericin B; Fluconazole
  
  **Aspergillus**: Amphotericin B; Voriconazole

**Hematopoietic growth factors:**
- G-CSF, only absolutely needed in case of planned stem cell transplantation for stem cell mobilization and collection – not to be used during treatment outlined below.

**Overview of Regimens**

**Standard Regimens for Acute Myelogenous Leukemia (AML) (excluding APML which is addressed separately and later in this document)**

**Induction Therapy (<60 yrs and fit patients >60 yrs)**

**7+3 Cytarabine and Daunorubicin (1-2 cycles)**

| Cytarabine | Continuous infusion IV | 100mg/m²/day x 7 days |
| Daunorubicin | Intravenous | 60 - 90 mg/m²/day x 3 days |

**Consolidation Therapy: HiDAC (2-4 cycles)**

- **Cytarabine** IV over 2-3 hrs 2-3 g/m² b.i.d D1,3,5 (*) in patients younger than 60 years
- **Cytarabine** IV over 1 hour 500mg/m² b.i.d D1-D6 in patients older than 60 years (**)

*For favorable karyotype or if allogeneic stem cell transplantation is not feasible or not available

** If allogeneic stem cell transplantation is not feasible or not available

**Note 1**: In patients >65 years may reduce daunorubicin dose to 45mg/m².

**Note 2**: In very frail patients consider low dose cytarabine, 5-azacitidine or hydroxyurea cytoreduction and BSC only.

**Note 3**: Allogeneic stem cell transplantation consolidation is not included due to limited availability, and the acknowledgement that where available there are likely to be greater resources and availability of necessary medicines and supportive care.

Note 4: Corticosteroid eyedrops essential with HiDAC.
Standard Regimen for Acute Promyelocytic Leukemia (APML)

**Induction Therapy**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATRA</td>
<td>45 mg/m^2</td>
<td>PO</td>
<td>Daily in divided doses until remission (All-trans retinoic acid)</td>
</tr>
<tr>
<td>Daunorubicin</td>
<td>60-90 mg/m^2</td>
<td>IV</td>
<td>Days 1-3</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>100-200 mg/m^2</td>
<td>IV</td>
<td>Days 1-7</td>
</tr>
</tbody>
</table>

**Consolidation Therapy**

**Option 1**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arsenic trioxide</td>
<td>0.15 mg/kg/day</td>
<td>IV</td>
<td>x 5 days for 5 wks</td>
</tr>
<tr>
<td>ATRA</td>
<td>45 mg/m^2</td>
<td>PO</td>
<td>x 7 days</td>
</tr>
<tr>
<td>Daunorubicin</td>
<td>50 mg/m^2</td>
<td>IV</td>
<td>x 3 days</td>
</tr>
</tbody>
</table>

Repeated for 2 cycles

**Option 2**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daunorubicin</td>
<td>60 mg/m^2</td>
<td>IV</td>
<td>days 1-3</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>100-200 mg/m^2</td>
<td>IV</td>
<td>days 1-7</td>
</tr>
</tbody>
</table>

For 1 cycle followed by:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytarabine*</td>
<td>2 gm/m^2</td>
<td>IV</td>
<td>q 12 hr x 5 days</td>
</tr>
<tr>
<td>Daunorubicin</td>
<td>45 mg/m^2</td>
<td>IV</td>
<td>days 1-3</td>
</tr>
</tbody>
</table>

(*Cytarabine dose = 1.5 mg/m^2 for patients > 60 years old)

**Note:** Idarubicin may be substituted for daunorubicin but is more costly. For example, in South Africa, a 10mg vial of idarubicin is 94USD, whereas a 20mg vial of daunorubicin is 6USD. Given that either drug may be used, and that daunorubicin is already on the EML and idarubicin is not, reviewers have not included idarubicin in the present recommendations.

Maintenance therapy:

ATRA 45mg/m^2 x 15 days po every 3 months
6-mercaptopurine 100mg/m^2 daily po
Methotrexate 10mg/m^2 weekly po

All x 2 years
**Review of Benefits and Harms**

**Overview**

Induction combination chemotherapy for AML with cytarabine and an anthracycline has been standard of care since late 1970s. Gale et al (3) showed an 82% CR rate in 68 patients receiving cytarabine, daunorubicin and 6-thioguanine (TAD). The median duration of remission was 13 months with median survival of 21 months. Rowe et al (4) showed no benefit with induction idarubicin or mitoxantrone versus daunorubicin in older AML patients suggesting that daunorubicin still remains the standard induction anthracycline.

As the high CR rate was not translated into long term survival, most subsequent studies have concentrated on consolidation therapy. Appelbaum et al (5), in a study of 111 patients in first CR, compared allogeneic transplantation in 44 patients with donors, 33 of whom received transplants, with 46 patients who received continued chemotherapy. The 5 year estimated DFS was 49% +/- 18% for the transplant group versus 20% +/- 13% for the chemotherapy group.

In 1994, Mayer et al (6) treated 1088 adult AML patients with induction cytarabine plus daunorubicin and then randomized the 693 patients in CR to 4 cycles of cytarabine at 100mg/m² CI x 5 days; 400mg/m² CI x 5 days; or 3g/m² over 3 hours bid D1, 3, 5 (HiDAC). All patients received 4 cycles maintenance cytarabine plus daunorubicin thereafter. At 52 months, the DFS compared to 100mg/m² was superior for 400mg/m² (HR 0.75, 95% CI 0.6-0.94) and HiDAC (HR 0.67, 95% CI 0.53-0.86). In patients under 60 years, the 4 year DFS rate was 24% versus 29% versus 44% respectively (p=0.002). Bloomfield et al (7) showed that patients receiving HiDAC in the same study with favorable karyotype had a 78% 5 year CR rate while those with normal karyotype had 40% 5 year CR rate. Patients receiving 400mg/m² with favorable karyotype had a 57% 5 year CR rate compared to 37% with normal karyotype. Patients with other abnormalities has 5 year CR rate <21% regardless of therapy given. Cassileth et al (8) compared HiDAC with autologous and allogeneic stem cell transplantation and found no significant difference in DFS and a marginal benefit for HiDAC versus autotransplantation (p=0.05) and allotransplantation (p=0.04).

Tallman et al (9) showed a 72% CR rate and 67% 3 year survival rate with ATRA plus chemotherapy in APML compared to 69% and 50% with cytarabine plus daunorubicin alone (p=0.003), showing that ATRA should be included in APL therapy. In 2011, Avvisati et al (10) showed a 94.3% CR rate with ATRA plus idarubicin induction and 3 cycles consolidation in APML. Patients who were t(15;17) negative on RT-PCR received maintenance ATRA +/- methotrexate/6MP. The 12 year EFS was 68.9% (95% CI, 66.4-71.4%) with no difference between 2 arms. In 2010, Powell et al (11) showed that the addition of As₂O₃ consolidation to induction with ATRA plus chemotherapy in APL improved 3 year EFS from 63% to 80% (p<0.0001) and 3 year OS from 81% to 86% (p=0.059).
Overall Benefits of AML Therapy

With remission induction chemotherapy:
• Up to 80% CR rate especially <60 years.

HiDAC Consolidation:
• Good risk karyotype: 60-80% 5 year CR rate.
• Intermediate risk karyotype: ~40% 5 year CR rate
• Poor risk karyotype: 10-20% 5 year CR rate (not recommended)

Harms and Toxicity Considerations

Common
Patients treated the regimens above will typically experience severe pancytopenia, which often may require blood and platelet transfusions. Pancytopenia is also associated with a high risk of infection and precautions to reduce exposure to pathogens should be taken and prophylaxis should be considered. [15] The chemotherapy combination commonly causes gastrointestinal damage resulting in mucositis and/or diarrhea in 10-25% of patients. [15] Other common chemotherapy-specific risks include fever or flu-like syndrome with cytarabine and alopecia associated with anthracyclines.

Approximately 26% of patients treated with ATRA, especially those with high baseline WBC, experience a retinoic acid-APL syndrome characterized by respiratory distress, fever, interstitial pulmonary infiltrates and pleural or pericardial effusions, which can be life threatening. However, in most cases the syndrome is reversible with a short course of dexamethasone.[9]

Serious
Potentially serious cardiotoxicity leading to congestive heart failure can be seen with anthracyclines including daunorubicin and idarubicin. Although transient changes in EKG may be observed, the risk of congestive heart failure is minimal particularly in the dose regimens used above.[16]

High-dose cytarabine (≥3 g/m² every 12 hours) can cause CNS toxicity including acute cerebellar syndrome in >10% of patients. Severe hemorrhagic conjunctivitis is also a complication of high dose cytarabine but can be prevented by corticosteroid eyedrops. Caution should be taken particularly when there is underlying abnormal renal or hepatic function.[17]

Systematic Reviews

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Highlights of article: “Prospective trials assigning adult patients with AML in CR1 to undergo allogeneic SCT vs nonallogeneic SCT treatment(s) based on donor availability. Overall, 24 trials and 6007 patients were analyzed; 3638 patients were analyzed by cytogenetic risk. Compared with nonallogeneic SCT, the HR of relapse or death with allogeneic SCT for AML in CR1 was 0.80 (95% CI, 0.74-0.86). Significant RFS benefit of allogeneic SCT was documented for poor-risk (HR, 0.69; 95% CI, 0.57-0.84) and intermediate-risk AML (HR, 0.76; 95% CI, 0.68-0.85) but not for good-risk AML (HR, 1.06; 95% CI, 0.80-1.42). The HR of death with allogeneic SCT for AML in CR1 was 0.90 (95% CI, 0.82-0.97). Significant overall survival benefit with allogeneic SCT was documented for poor-risk (HR, 0.73; 95% CI, 0.59-0.90) and intermediate-risk AML (HR, 0.83; 95% CI, 0.74-0.93) but not for good-risk AML (HR, 1.07; 95% CI, 0.83-1.38). CONCLUSION: Compared with nonallogeneic SCT therapies, allogeneic SCT has significant RFS and overall survival benefit for intermediate- and poor-risk AML.”

Recommendations
The reviewers recommend the incorporation of AML and APL treatment options into the WHO Model List of Essential Medicines, and recommend specifically that ATRA and arsenic trioxide be added to the core Essential Medicines List. Although drugs needed for induction and consolidation chemotherapy can be accessed in both low and middle income countries (LICs and MICs), AML including APML cannot be treated in a vacuum. Unless blood products, isolation facilities, ICU support as well as hematology and molecular laboratory as well as radiology support is available, appropriate definitive treatment is not feasible.

1. Countries without adequate blood products, supportive care, laboratory and radiology support: Patients should be referred to countries with those resources.
2. Countries with adequate support services but unsafe blood products: Patients should be referred to countries with safe blood products.
3. Countries with adequate support and safe blood products: Patients should receive induction cytarabine plus daunorubicin followed by high dose cytarabine consolidation in patients with favorable and intermediate risk karyotype achieving complete remission (See “Koreth J et al. JAMA 2009” in Systematic Reviews above). Salvage chemotherapy is not recommended in the absence of allogeneic stem cell transplant facilities.
4. Countries with adequate support, safe blood products and allotransplant facilities: Patients should receive induction cytarabine plus daunorubicin (or idarubicin). High dose cytarabine consolidation in good and intermediate risk patients with possible allogeneic stem cell transplantation in high risk and intermediate risk patients with available matched donors achieving remission. Salvage chemotherapy should only be recommended in patients with available donors and allotransplant facilities.
5. Patients with APML should receive induction ATRA plus daunorubicin or idarubicin followed by consolidation cycles with anthracyclines and ATRA. Maintenance ATRA +/- 6MP/methotrexate. As2O3 should be considered only if readily available.

Additions proposed for Section 8.2 of the EML

ATRA
Arsenic Trioxide
References
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16. Floyd J, Morgan JP. Cardiotoxicity of anthracycline-like chemotherapy agents. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA.
17. Lee EQ, Wen PY. Overview of neurologic complications of non-platinum cancer chemotherapy. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA.