

Acute myelogenous leukaemia (AML) including Acute promyelocytic leukaemia (APML) – EML

The application sought endorsement of cytarabine and daunorubicin, already listed on the Model List, for the treatment of acute myelogenous leukaemia (AML) and acute promyelocytic leukaemia (APML) as induction and consolidation therapy. The application also sought the addition of all-*trans* retinoic acid (ATRA) and arsenic trioxide to the Model List as induction therapy for APML, and the endorsement of 6-mercaptopurine and methotrexate, already listed on the Model List, for maintenance therapy of APML.

The application, amended to include details of the Expert Committee's considerations and decision, is presented in this section.

Introduction

AML is a heterogeneous haematological 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; 54% of patients are aged over 65 years and 33% over 75 years (1). Among patients 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 leukaemia incidence for 2012 to be 351 965, with an age-standardized rate (ASR) of 4.7 per 100 000 per year, a 5-year prevalence of 1.5% and a male:female ratio of approximately 1:4 (2). In countries with a medium level value on the Human Development Index (HDI),¹ the 2012 ASR was 3.8 per 100 000 per year; in countries with a low level value on the HDI it was 2.5 per 100 000 per year. Mortality was 265 461 worldwide, with an ASR of 3.4 per 100 000 per year. The ASR was higher (3.2 per 100 000) in countries with "medium human development" than in countries of "low human development" (2.4 per 100 000). Unfortunately, the International Agency for Research on Cancer (IARC) does not sub-classify leukaemias into acute and chronic, and myeloid or lymphoid, in its GLOBOCAN analysis.

¹ See: <http://hdr.undp.org/en/content/human-development-index-hdi>.

Classification

Currently, AML is classified as follows, using the WHO classification of 2008 (3), which replaces the French–American–British (FAB) classification and an earlier (2001) WHO classification:

Acute myeloid leukaemia 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(9;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); RBM15-MKL1

Provisional entity: AML with mutated NPM1

Provisional entity: AML with mutated CEBPA

Acute myeloid leukaemia with myelodysplasia-related changes

Therapy-related myeloid neoplasms

Acute myeloid leukaemia, not otherwise specified

AML with minimal differentiation

AML without maturation

AML with maturation

Acute myelomonocytic leukaemia

Acute monoblastic/monocytic leukaemia

Acute erythroid leukaemia

Pure erythroid leukaemia

Erythroleukaemia, erythroid/myeloid

Acute megakaryoblastic leukaemia

Acute basophilic leukaemia

Acute panmyelosis with myelofibrosis

Myeloid sarcoma

Myeloid proliferations related to Down syndrome

Transient abnormal myelopoiesis

Myeloid leukaemia associated with Down syndrome

Blastic plasmacytoid dendritic cell neoplasm

Prognostic factors for AML

Cytogenetic and genetic factors: chromosome and gene abnormalities

Favourable 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.

Unfavourable 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. One in three 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 *CEBP α* gene (so called biallelic gene mutations).

Based on cytogenetics and the novel molecular parameters, updated prognostic risk group stratification for AML has been described. The European LeukemiaNet standardized reporting for correlation of cytogenetic and molecular genetic data in AML with clinical data is shown in Table 6 (4).

Table 6

European LeukemiaNet standardized reporting for correlation of cytogenetic and molecular genetic data in AML with clinical data

Favourable	t(8;21)(q22;q22); RUNX1-RUNX1T1 inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFβ-MYH11 Mutated NPM1 without <i>FLT3</i> -ITD (normal karyotype) Mutated CEBPA (normal karyotype)
Intermediate-I	Mutated NPM1 and <i>FLT3</i> -ITD (normal karyotype) Wild-type NPM1 and <i>FLT3</i> -ITD (normal karyotype) Wild-type NPM1 without <i>FLT3</i> -ITD (normal karyotype)
Intermediate-II	t(9;11)(p22;q23); MLLT3-MLL Cytogenetic abnormalities not classified as favourable or adverse
Adverse	inv(3)(q21q26.2) or t(3;3)(q21;q26.2); RPN1-EVI1 t(6;9)(p23;q34); DEK-NUP214 t(v;11)(v;q23); MLL rearranged -5 or del(5q); -7; abn(17p); complex karyotype ^a

^a Defined as three or more chromosome abnormalities in the absence of one of the WHO-designated recurring translocations or inversions, that is, t(15;17), t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23), t(6;9), inv(3) or t(3;3).

Clinical markers of prognosis

Age:

Older patients (over 60 years) do not fare as well as younger patients: they are more likely to have unfavourable chromosome abnormalities as well as comorbid medical conditions that can make it more difficult 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 haematological disorders (e.g. polycythaemia vera or marrow failure syndromes (Fanconi, congenital neutropenia and others) and myelodysplastic syndromes are linked to a poor outcome of AML.

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

Definitive diagnosis of AML requires laboratory access:

Peripheral blood:

- A phlebotomist (nurse, physician or laboratory technician) is required to draw peripheral blood and make smears from a patient presenting with one or more of anaemia, abnormal bleeding and infection.
- A trained laboratory technician with access to a haematology counter is required to establish the initial diagnosis by demonstrating a low/normal/high white blood cell count with a low platelet count and anaemia.
- A trained haematologist is required to confirm the diagnosis by identifying “blast cells” in peripheral blood smears and to plan a bone marrow aspiration and biopsy.

Bone marrow aspiration and biopsy:

- Bone marrow aspirates are part of the routine evaluation of AML. Whenever 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 haematopathologist are needed for morphological evaluation of 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.
- Fluorescence in situ hybridization may substitute only for specific cytogenetic abnormalities for which probes are available but it does not provide a complete karyotype. It is more sensitive than conventional cytogenetics testing and is employed when certain aberrations are suspected.
- Real-time polymerase chain reaction is the most sensitive assay for demonstrating translocations or certain molecular aberrations such as *FLT-3*, *NPM1* and *CEBP α* .
- DNA sequencing is needed to demonstrate certain subtle mutations.

Monitoring

Definitive diagnostic tests:

- Complete blood count (CBC), clotting parameters (international normalized ratio, partial thromboplastin time), liver and kidney function tests, uric acid, bone marrow aspirate.
- In certain cases, cytogenetics and sequencing may also be necessary.

Supportive testing:

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

Follow-up testing:

- CBC and clotting parameters (daily), renal and liver functions (2–7 times weekly), microbiology (as needed), radiology (as needed), bone marrow aspiration and biopsy (after every remission-induction cycle and consolidation and thereafter every 6 months and when indicated because of suspected or possible relapse), cytogenetic/molecular testing as needed.

Administration and care of patients

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

Supportive care

Blood products:

- Red blood cells, preferably filtered to remove contaminating white blood cells from the red cell concentrate or irradiated.
- Platelets: pheresis (preferred) and pooled.
- Fresh-frozen plasma – 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 included to acknowledge that patients undergoing treatment for AML are at high risk for many infections, caused by a variety of organisms, some of which may be resistant to multiple antibiotics. The availability of a wide spectrum of antibiotics can improve outcome for these patients. The following are some examples of infectious etiologies for these patients and the antibiotics that can be used to treat them; some of the antibiotics are not currently on the EML.

- Gram-negative bacilli, e.g. *Klebsiella*, *Pseudomonas*:
Sensitive: piperacillin/tazobactam; cefipime; ceftazidime; ertapenem
Extended-spectrum beta-lactamases: meropenem; imipenem
Carbapenem-resistant Enterobacteriaceae: colimycin; tigecycline
- Gram-positive cocci, e.g. *Staphylococcus*, *Streptococcus*
Sensitive: amoxicillin/clavulinate; cloxacillin
Methicillin-resistant Staphylococcus aureus: vancomycin; linezolid
- Fungi, e.g. *Candida*, *Aspergillus*
Candida: amphotericin B; fluconazole
Aspergillus: amphotericin B; voriconazole

Haematopoietic growth factors:

- Granulocyte colony-stimulating factor – absolute need only in case of planned stem cell transplantation for stem cell mobilization and collection – not to be used during the treatment outlined below.

Overview of regimens

Standard regimens for AML (excluding APML)

- **Induction therapy (<60 years and fit patients >60 years): 7+3 cytarabine and daunorubicin (1–2 cycles)**
 - cytarabine 100 mg/m² per day continuous IV infusion x 7 days
 - daunorubicin 60–90 mg/m² per day IV x 3 days
- **Consolidation therapy: HiDAC (2–4 cycles)**
 - cytarabine 2–3 g/m² IV over 2–3 hours twice daily on days 1, 3 and 5 (patients <60 years)
 - cytarabine 500 mg/m² IV over 1 hour twice daily on days 1–6 (patients >60 years).

Notes:

1. In patients >65 years, daunorubicin dose may be reduced to 45 mg/m².

2. In very frail patients consider low-dose cytarabine, 5-azacitidine or hydroxyurea cytoreduction and best supportive care only.
3. Allogeneic stem cell transplantation consolidation is not included because of limited availability and the fact that, where it is available, resources are likely to be greater and necessary medicines and supportive care available.
4. Corticosteroid eye drops are essential with HiDAC.

Standard regimen for APML

- **Induction therapy**

- ATRA 45 mg/m² per day orally in divided doses until remission
- daunorubicin 60–90 mg/m² IV on days 1–3
- cytarabine 100–200 mg/m² IV on days 1–7

- **Consolidation therapy**

- *Option 1*

- arsenic trioxide 0.15 mg/kg per day IV x 5 days for 5 weeks
- ATRA 45 mg/m² per day orally x 7 days
- daunorubicin 50 mg/m² IV x 3 days

Repeated for 2 cycles.

- *Option 2*

- daunorubicin 60 mg/m² IV on days 1–3
- cytarabine² 100–200 mg/m² IV on days 1–7

for 1 cycle followed by:

- cytarabine 2 g/m² IV every 12 hours x 5 days
- daunorubicin 45 mg/m² IV on days 1–3

- **Maintenance therapy**

- ATRA 45 mg/m² orally x 15 days every 3 months
- 6-mercaptopurine 100 mg/m² per day orally
- methotrexate 10 mg/m² orally weekly

All x 2 years.

Review of benefits and harms

Overview

Induction combination chemotherapy for AML with cytarabine and an anthracycline has been the standard of care since the late 1970s. Gale et al. showed an 82% complete remission rate in 68 patients receiving high-dose induction chemotherapy with cytarabine, daunorubicin and 6-thioguanine; median duration of remission was 13 months and median survival 21 months (5). Rowe et al. found no benefit with induction idarubicin or mitoxantrone versus daunorubicin in older AML patients, suggesting that daunorubicin

² Cytarabine dose = 1.5 g/m² for patients >60 years old.

remains the standard induction anthracycline (6). However, subsequent meta-analyses that included this and other randomized controlled trials showed a slight advantage of idarubicin over daunorubicin or other anthracyclines, when used with cytosine arabinoside as induction chemotherapy for newly diagnosed AML, particularly in younger patients (7, 8). The number of trials was limited, however, with some heterogeneity of effects between trials, and the differences between idarubicin and daunorubicin were not large; careful interpretation of the results is thus necessary.

Because the high complete remission rate was not translated into long-term survival, most subsequent studies have concentrated on consolidation therapy. Mayer et al. treated 1088 adult AML patients with induction cytarabine plus daunorubicin and then randomized the 693 patients in complete remission to different doses of cytarabine (9). All patients received four cycles of maintenance cytarabine plus daunorubicin thereafter. At 52 months, the probability of remaining disease-free was higher in the group treated with higher doses (3 g/m² over 3 hours twice daily on days 1, 3 and 5 (HiDAC)). In patients under 60 years of age, the 4-year disease-free survival rate was 24% for the 100 mg/m² group compared with 29% and 44% for the 400 mg/m² and HiDAC groups respectively. Notably, less than 30% of elderly patients were able to complete four cycles of maintenance therapy because of toxicity. Bloomfield et al. analysed a subgroup of patients of the same study (10). They showed that 5-year complete remission rate for patients receiving HiDAC was 78% for those with favourable karyotype compared with 40% for those with normal karyotype; in patients receiving 400 mg/m², 5-year complete remission rate was 57% for those with favourable karyotype compared with 37% for those with normal karyotype. The 5-year complete remission rate for patients with other abnormalities was less than 21%, regardless of therapy given.

In a study by Appelbaum et al., 111 patients with newly diagnosed acute non-lymphoblastic leukaemia were treated with induction chemotherapy. In the 90 patients who achieved complete remission, the outcome of marrow transplantation was compared with that of continued chemotherapy: 33 of 44 patients who had available donors received transplants, while 46 patients without histocompatible donors received continued chemotherapy (11). Estimates of 5-year disease-free survival were higher for the transplant group than for the chemotherapy group. A recent Cochrane systematic review included results from 14 trials and 3157 patients (12). The meta-analysis for overall survival showed the superiority of the donor versus no donor group with a hazard ratio (HR) of 0.86 (95% CI: 0.77–0.97; *P* = 0.01), and no significant heterogeneity between trials.

Cassileth et al. compared HiDAC with autologous and allogeneic stem cell transplantation for adults with AML in first remission who did not have a histocompatible sibling donor (13). They found no significant difference in disease-free survival and a marginal benefit for HiDAC versus autotransplantation and allotransplantation. This result was confirmed in a meta-analysis that compared the efficacy of consolidation therapy with autologous bone marrow transplantation versus non - myeloablative chemotherapy alone or no further treatment following induction therapy (14). The ratio of overall survival

probabilities was 1.01 (95% CI: 0.89–1.15; $P = 0.86$). However, autologous bone marrow transplantation was associated with a statistically significant greater risk of death during first remission (odds ratio from 6 studies 2.63; 95% CI: 1.6–4.32; $P < 0.001$).

In a three-year American inter-group study involving 346 patients with previously untreated APLM, three courses of chemotherapy were compared with ATRA treatment followed by two courses of chemotherapy (15). The incidence of relapse was significantly reduced in patients who received ATRA (33% versus 68% at 3 years, $P < 0.01$); overall survival was also better in the ATRA group (50% versus 67% at 3 years, $P < 0.003$). In a systematic review exploring efficacy and safety of maintenance therapy in APLM patients, maintenance with ATRA alone improved disease-free survival compared with observation (HR 0.47; 95% CI: 0.33–0.66); ATRA-containing regimens (ATRA alone or ATRA combined with chemotherapy) compared with observation achieved a significantly better disease free-survival (HR 0.48; 95% CI: 0.35–0.66); and in maintenance treatment, ATRA-based regimens were also associated with improved disease-free survival compared with non-ATRA-based regimens (HR 0.72; 95% CI: 0.51–1.01) (16). Results for overall survival were less straightforward.

In 2010, Powell et al. showed that the addition of arsenic trioxide (As_2O_3) consolidation to induction with ATRA plus chemotherapy in APLM improved 3-year event-free survival from 63% to 80% ($P < 0.0001$) and 3-year overall survival from 81% to 86% ($P = 0.059$) when compared with two courses of consolidation therapy with ATRA plus daunorubicin (17). Other randomized controlled trials explored the efficacy and safety of As_2O_3 consolidation compared with different controls (18), but data on comparison with the current standard treatment regimen (ATRA plus chemotherapy) are lacking.

Overall benefits of AML therapy

With remission induction chemotherapy:

- Up to 80% complete remission (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 with the regimens described above will typically experience severe pancytopenia, often requiring blood and platelet transfusions. Pancytopenia is also associated with a high risk of infection; precautions should be taken to reduce exposure to pathogens and prophylaxis should be considered. The chemotherapy combination commonly causes gastrointestinal damage, resulting in mucositis and/or diarrhoea in 10–

25% of patients (19). Other common chemotherapy-specific risks include fever or influenza-like syndrome with cytarabine and alopecia associated with anthracyclines.

Approximately 26% of patients treated with ATRA, especially those with high baseline white blood cell count, experience a retinoic acid syndrome characterized by respiratory distress, fever, interstitial pulmonary infiltrates and pleural or pericardial effusions, which can be life-threatening. In most cases, however, the syndrome is reversible with a short course of dexamethasone (15). Increased rates of grade 3/4 adverse events have been reported for any maintenance treatment compared with observation, as well as for maintenance combining ATRA and chemotherapy compared with ATRA alone, which may limit patient adherence to treatment (16).

Serious

Potentially serious cardiotoxicity leading to congestive heart failure can be seen with anthracyclines, including daunorubicin and idarubicin. Although transient changes in the electrocardiogram may be observed, the risk of congestive heart failure is minimal, particularly in the dose regimens described above (20).

High-dose cytarabine (≥ 3 g/m² every 12 hours) can cause central nervous system toxicity, including acute cerebellar syndrome in >10% of patients. Severe haemorrhagic conjunctivitis is also a complication of high-dose cytarabine but can be prevented by corticosteroid eye drops. Caution should be exercised, particularly when there is underlying abnormal renal or hepatic function (21).

Recommendations

The Expert Committee agreed that, although drugs needed for induction and consolidation chemotherapy for AML and APML can be accessed in both low- and middle-income countries, these conditions cannot be treated in a vacuum. Unless safe blood products, isolation facilities, and intensive care support, as well as haematology and molecular laboratory and radiology support, are available, appropriate definitive treatment is not feasible and consideration may need to be given to referring patients to centres (or even countries) that have these resources.

Where these critical resources are available, the Committee agreed that induction treatment for AML with cytarabine plus daunorubicin (or idarubicin), followed by high-dose cytarabine consolidation therapy, demonstrates relevant clinical benefit in patients with favourable and intermediate-risk karyotype (5-year CR rate of 60–80% and approximately 40%, respectively). The Committee also agreed that salvage chemotherapy should be recommended only in settings where there are allogeneic stem cell transplant facilities.

For patients with APML, the Committee agreed that induction treatment with ATRA plus daunorubicin (or idarubicin), followed by consolidation cycles with anthracyclines and ATRA, is associated with a relevant clinical benefit (17% increase in 3-year survival). In the

maintenance setting, ATRA – with or without 6-mercaptopurine and methotrexate – is also associated with benefit.

The Committee noted that addition of arsenic trioxide as consolidation therapy for APML does not produce a clinically relevant increase in overall survival in naïve patients. The Committee also noted the extremely high price and low availability of arsenic trioxide, and considered that this would be unaffordable in many low- and middle-income countries.

On the basis of the available evidence, the Expert Committee made the following overall recommendations:

- cytarabine and daunorubicin, currently on the complementary list, should be specifically endorsed for the treatment of AML;
- cytarabine, daunorubicin, mercaptopurine and methotrexate, currently on the complementary list, should be specifically endorsed for the treatment of APML;
- all-trans retinoic acid (ATRA) should be added to the complementary list for the treatment of APML;
- arsenic trioxide should not be added to the EML for treatment of APML.

1. Acute myeloid leukemia, Version 2. 2014. Fort Washington, PA: National Comprehensive Cancer Network; 2014 (NCCN Clinical Practice Guidelines in Oncology).
2. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013 [Available from: <http://globocan.iarc.fr>].
3. WHO classification of tumours of haematopoietic and lymphoid tissues. Fourth ed. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al., editors. Lyon: International Agency for Research on Cancer; 2008.
4. Dohner H, Estey EH, Amadori S, Appelbaum FR, Buchner T, Burnett AK, et al. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. *Blood*. 2010;115(3):453-74.
5. Gale RP, Foon KA, Cline MJ, Zigelboim J. Intensive chemotherapy for acute myelogenous leukemia. *Ann Intern Med*. 1981;94(6):753-7.
6. Rowe JM, Neuberg D, Friedenberg W, Bennett JM, Paietta E, Makary AZ, et al. A phase 3 study of three induction regimens and of priming with GM-CSF in older adults with acute myeloid leukemia: a trial by the Eastern Cooperative Oncology Group. *Blood*. 2004;103(2):479-85.
7. Wang J, Yang YG, Zhou M, Xu JY, Zhang QG, Zhou RF, et al. Meta-analysis of randomised clinical trials comparing idarubicin + cytarabine with daunorubicin + cytarabine as the induction chemotherapy in patients with newly diagnosed acute myeloid leukaemia. *PLoS One*. 2013;8(4):e60699.
8. A systematic collaborative overview of randomized trials comparing idarubicin with daunorubicin (or other anthracyclines) as induction therapy for acute myeloid leukaemia. AML Collaborative Group. *Br J Haematol*. 1998;103(1):100-9.

9. Mayer RJ, Davis RB, Schiffer CA, Berg DT, Powell BL, Schulman P, et al. Intensive postremission chemotherapy in adults with acute myeloid leukemia. Cancer and Leukemia Group B. *N Engl J Med*. 1994;331(14):896-903.
10. Bloomfield CD, Lawrence D, Byrd JC, Carroll A, Pettenati MJ, Tantravahi R, et al. Frequency of prolonged remission duration after high-dose cytarabine intensification in acute myeloid leukemia varies by cytogenetic subtype. *Cancer Res*. 1998;58(18):4173-9.
11. Appelbaum FR, Dahlberg S, Thomas ED, Buckner CD, Cheever MA, Clift RA, et al. Bone marrow transplantation or chemotherapy after remission induction for adults with acute nonlymphoblastic leukemia. A prospective comparison. *Ann Intern Med*. 1984;101(5):581-8.
12. Pidala J, Djulbegovic B, Anasetti C, Kharfan-Dabaja M, Kumar A. Allogeneic hematopoietic cell transplantation for adult acute lymphoblastic leukemia (ALL) in first complete remission. *Cochrane Database Syst Rev*. 2011(10):CD008818.
13. Cassileth PA, Harrington DP, Appelbaum FR, Lazarus HM, Rowe JM, Paietta E, et al. Chemotherapy compared with autologous or allogeneic bone marrow transplantation in the management of acute myeloid leukemia in first remission. *N Engl J Med*. 1998;339(23):1649-56.
14. Nathan PC, Sung L, Crump M, Beyene J. Consolidation therapy with autologous bone marrow transplantation in adults with acute myeloid leukemia: a meta-analysis. *J Natl Cancer Inst*. 2004;96(1):38-45.
15. Tallman MS, Andersen JW, Schiffer CA, Appelbaum FR, Feusner JH, Ogden A, et al. All-trans-retinoic acid in acute promyelocytic leukemia. *N Engl J Med*. 1997;337(15):1021-8.
16. Muchtar E, Vidal L, Ram R, Gafter-Gvili A, Shpilberg O, Raanani P. The role of maintenance therapy in acute promyelocytic leukemia in the first complete remission. *Cochrane Database Syst Rev*. 2013;3:CD009594.
17. Powell BL, Moser B, Stock W, Gallagher RE, Willman CL, Stone RM, et al. Arsenic trioxide improves event-free and overall survival for adults with acute promyelocytic leukemia: North American Leukemia Intergroup Study C9710. *Blood*. 2010;116(19):3751-7.
18. Xu SN, Chen JP, Liu JP, Xia Y. [Arsenic trioxide in combination with all-trans retinoic acid for acute promyelocytic leukemia: a systematic review and meta-analysis]. *Zhong Xi Yi Jie He Xue Bao*. 2009;7(11):1024-34.
19. Larson RA. Induction therapy for acute myeloid leukemia in younger adults. In: *UpToDate [website]*. Waltham, MA: UpToDate; 2014.
20. Floyd J, Morgan JP. Cardiotoxicity of anthracycline-like chemotherapy agents. In: *UpToDate [website]*. Waltham, MA: UpToDate; 2014.
21. Lee EQ, Wen PY. Overview of neurologic complications of non-platinum cancer chemotherapy. In: *UpToDate [website]*. Waltham, MA: UpToDate; 2014.