



Guideline 12-9 REQUIRES UPDATING

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Systemic Treatment of Acute Myeloid Leukemia (AML)

Members of the Acute Leukemia Advisory Committee

Guideline 12-9 was reviewed in February 2019 and the Acute Leukemia Advisory Committee determined that it **REQUIRES UPDATING**.
(See Section 6: Document Assessment and Review for details)

Guideline 12-9 is comprised of 6 sections. You can access the summary and full report here: <https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/28266>

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February 28, 2019

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PEBC Report Citation (Vancouver Style): Schuh AC, Fletcher GG, Leber B, Sabloff M, and members of the Hematology Disease Site Group. Systemic treatment of acute myeloid

leukemia (AML). Bredeson C, Yee K, Durocher-Allen LD, reviewers. Toronto (ON): Cancer Care Ontario; 2016 Feb 2 [REQUIRES UPDATING 2019 Feb]. Program in Evidence-Based Care Guideline No.:12-9 REQUIRES UPDATING.

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IN REVIEW

Guideline Report History

| GUIDELINE VERSION | SYSTEMATIC REVIEW | | PUBLICATIONS | NOTES and KEY CHANGES |
|--------------------------------------|---------------------|--|----------------------------|---|
| | Search Dates | Data | | |
| Original version February 2016 | 2006 to Aug 2015 | Full Report | Web publication | NA |
| Current Version February 2019 | 2015 to Mar 2018 | New data found in Section 6: Document Assessment and Review | Updated web publication | 2016 recommendations REQUIRE UPDATING |

SYSTEMIC TREATMENT OF ACUTE MYELOID LEUKEMIA (AML)

Section 1: Recommendations Summary

The 2016 recommendations

REQUIRE UPDATING

This means that the guidance document needs updating to ensure that the recommendations reflect current evidence and practice. The existing recommendations remain relevant and it is still appropriate for this document to be available while the updating process unfolds.

GUIDELINE OBJECTIVES

The primary objective was to make recommendations regarding the most effective intensive systemic treatment of acute myeloid leukemia (AML) in adult patients. A secondary objective was to make recommendations regarding use of patient characteristics to determine appropriate treatment.

TARGET POPULATION

The target population is adult patients with AML (excluding acute promyelocytic leukemia) who are deemed suitable for intensive treatment.

INTENDED USERS

The intended users are hematologists, oncologists, nurses, and pharmacists.

RESEARCH QUESTIONS

1. What is the most effective systemic induction treatment for adults with previously untreated AML who can tolerate intensive treatment?
2. What is the most effective systemic post-remission treatment (consolidation and/or maintenance, excluding stem cell transplant) for adults with previously untreated AML?
3. What is the most effective systemic treatment (reinduction, consolidation, maintenance; not including stem cell transplant) for adults with relapsed or refractory AML who can tolerate intensive treatment?
4. Which patient characteristics are most important when making treatment decisions?

RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE

Preamble

After reviewing the literature to arrive at these recommendations there are two important background issues that will affect their implementation:

1. Fitness or frailty is a key determinant in assessing whether a patient should be offered induction chemotherapy with curative intent because of the potential toxicity of this approach. The selection criteria for entry into most of the studies mentioned do not explicitly address this issue other than age and performance status. In studies specifying young or elderly patients, the cut-off is often 60 years of age, but 50 to 65 years have been used in some trials. It is becoming clear that age alone is not an accurate way of determining treatment tolerability and other tools are emerging that may refine the evaluation of this important factor. These types of studies are either in progress or in design and will hopefully better define the target population for these recommendations (1).
2. Due to the complex nature of treatment of AML and the heterogeneous way in which it is treated in different countries, these recommendations must be considered in the broader context of the jurisdiction in which the treatments were administered. For example, comparing the outcomes of different induction regimens may depend on when bone marrow evaluations were performed to confirm treatment response, and the number of induction courses that are considered standard (one versus two). Dosing of agents may also be influenced by the other agents used in the regimen. Similarly, the outcomes of consolidation regimens may be influenced by the preceding induction regimen, which is not uniform.

Question 1. Induction for Previously Untreated AML

Recommendation 1

- Cytarabine (cytosine arabinoside, AraC) plus an anthracycline (or anthracenedione) is recommended as standard induction treatment for AML.
 - Conventional-dose AraC at 100-200 mg/m²/day for seven days is recommended for routine use
 - High-dose AraC (HDAC) (1-3 g/m²/day) may be considered in younger patients and those with poor-risk factors*.
 - Idarubicin (IDA), daunorubicin (DNR), and mitoxantrone (MTZ), are the recommended anthracyclines (anthracenediones) for use with AraC.
 - The recommended dose for DNR is 60 mg/m²/day.
 - It is recommended that IDA or DNR be administered for three days. Various regimens with MTZ have been used and are considered acceptable.

*See Preamble above for age considerations and Background (Section 2) for a summary of the European LeukemiaNet subgroups (2)

Recommendation 2

Addition of gemtuzumab ozogamicin (GO) at 3 mg/m² to 7+3 regimens is recommended.

Qualifying Statements for Recommendation 2

- Increase in veno-occlusive disease (more recently designated sinusoidal obstructive syndrome [SOS]) has been reported with GO at 6 mg/m² (3,4). This was not evident

with doses at 3 mg/m². The risk of SOS needs to be weighed against the benefit of receiving GO in patients who are destined to receive an allogeneic cell transplant.

- While the ALFA-0701 trial (5) suggested greater benefit in patients with cytogenetically normal or with favourable/intermediate genetics, there was insufficient evidence to restrict the recommendation based on cytogenetics or other defined subgroups.
- While evidence indicates GO may improve OS and RFS, it is currently not approved for use in Canada.

Recommendation 3

The purine analogues cladribine, fludarabine, and clofarabine cannot be recommended for routine use at this time.

There may be a role in relapsed/refractory AML (see Question 3).

Qualifying Statements for Recommendation 3

- Some fludarabine regimens have been found effective but not directly compared with the same regimens without fludarabine, nor to standard 3+7 treatment. The MRC AML15 trial (6,7) and Russo et al (8,9) found benefit of FLAG-IDA (fludarabine + AraC + granulocyte colony-stimulating factor [GCSF] + IDA) and FLAI (fludarabine + AraC + IDA), respectively. The fludarabine arms contained high-dose AraC and the control arms used standard-dose AraC. The relative effect of AraC dose and fludarabine in these trials is unknown.
- FLAG is among the regimens recommended by (10) for relapsed/refractory AML based on non-randomized trials. A small Chinese study of induction (11) found FLAG (fludarabine + AraC + GCSF) and IDA + AraC to result in similar complete remission (CR). While evidence from the literature review is considered insufficient to make a recommendation, FLAG may be an option in cases where an anthracycline is contraindicated.

Recommendation 4

- Addition of etoposide to AraC plus DNR induction is not recommended.

Recommendation 5

- Induction chemotherapy adjuvants such as GCSF or granulocyte-macrophage (GM)-CSF, interleukin-11, or multidrug resistance modulators such as cyclosporine A, PSC-833 (valspodar), and zosuquidar are not recommended.

Question 2. Post-Remission Treatment

It is considered standard practice to give consolidation treatment to patients who achieve CR after induction treatment. Transplantation was outside the scope of the review and other guidelines should be consulted concerning appropriate selection of patients for transplant. All patients that may be transplant candidates should receive early referral to a transplant centre. While transplant may take place immediately after induction (without any

consolidation), due to delays prior to transplant, most patients scheduled for transplant will receive consolidation treatment.

Recommendation 6

Two or three courses of consolidation are recommended.

Qualifying Statements for Recommendation 6

- Regimens for consolidation may be the same as used for induction and the distinction between these two phases of treatment is sometimes somewhat arbitrary. The total number of courses of induction plus consolidation combined may be the most important consideration.

Recommendation 7

- For patients with core-binding factor (CBF)-AML receiving consolidation with AraC alone, HDAC at 1-3 g/m²/day is recommended. HDAC may be considered for other patients.
- Patients with CBF-AML should receive three cycles of consolidation, of which at least two contain HDAC.

Qualifying Statements for Recommendation 7

- HDAC at 1-3 g/m²/day is considered appropriate; however, there is insufficient evidence to recommend an optimal dose within this range.
- The benefit of HDAC is greatest for CBF-AML. The relative benefit of HDAC compared with adverse effects is less clear for other subtypes of AML.

Recommendation 8

- HDAC or standard-dose AraC may be used in combination chemotherapy. Standard-dose combination chemotherapy should be considered for patients determined to be unsuitable for HDAC consolidation.

Qualifying Statements for Recommendation 8

- Effectiveness may be influenced by age and/or prior treatment.
- There is insufficient evidence to recommend an optimal dose of HDAC.
- The benefit of adding anthracycline to HDAC is unclear.

Recommendation 9

- There is insufficient evidence to make any recommendations for or against the use of maintenance chemotherapy in patients who received consolidation therapy.
- Use of maintenance treatment alone is not routine, but may be considered for those unable to tolerate consolidation.

Qualifying Statements for Recommendation 9

- We did not consider there to be sufficient evidence to make a recommendation at this time. Based on past experience there is no evidence maintenance therapy after consolidation is useful as it currently exists; however, there are ongoing studies examining this issue (see Table 4-17). Ongoing trials with new drugs with different mechanisms of action and targeted therapy may find a benefit.

Question 3. Relapsed or Refractory AML

While the intent in the treatment of relapsed or refractory AML is to allow subsequent transplant for responding patients, the decisions regarding transplant eligibility and procedures are beyond the scope of this document. The Program in Evidence-Based Care/Cancer Care Ontario report on Stem Cell Transplant (12) and recent provincial guidelines should be consulted. All patients that may be transplant candidates should receive early referral to a transplant centre.

Recommendation 10

- For patients with refractory disease or relapse, a more intensive or non-cross-resistant treatment is recommended. The following list is not meant to be inclusive of all reasonable therapies, but highlights a few with good response in the included randomized controlled trials (RCTs):
 - HDAC + MTZ
 - AraC (500 mg/m²/day continuous infusion)* + MTZ + etoposide ± GM-CSF
 - AraC (100 mg/m² q12h) + DNR + etoposide
 - Low-dose CAG: AraC (10 mg/m² q12h) + ACR + GCSF ± etoposide

*See qualifying statement regarding dose

- Clofarabine, fludarabine (FLAG, FLAG-IDA), and cladribine regimens should be considered when alternative or additional agents are required.

Qualifying Statements for Recommendation 10

- There is no clear consensus about the length of CR duration that indicates re-treatment with the same induction chemotherapy would be as effective as an alternate regime. The National Comprehensive Cancer Network (NCCN) suggests CR duration of >12 months (10), while others use two to five years, or never. It has been suggested that AML recurring after a long CR may actually be new disease. With more detailed characterization of the genetic architecture of AML this distinction may become more evident in the near future. Re-treating with an ineffective regimen delays effective treatment while increasing risk of adverse events and treatment-related mortality.

- FLAG is among the regimens recommended by the NCCN (10) for relapsed/refractory AML based on non-randomized trials (13). While evidence from the literature review is considered insufficient to make a recommendation, FLAG may be an option in cases where an anthracycline is contraindicated.
- AraC at 1 g/m²/day or 1.5 g/m²/day has also been widely used (e.g., (14-16)) but not directly compared. Several trials, both randomized and retrospective, report a large variation in response rates (17-22).
- A small case-series reported experience using high-dose etoposide and cyclophosphamide with modest benefit (23), although evidence appears weak.

Question 4. Which patient characteristics are most important when making treatment decisions?

During the planning stages of the systematic review it was decided to focus on RCTs, while acknowledging that RCTs might not provide the best source of evidence on patient characteristics. Some treatments were found to be of benefit in only a subset of patients (age, cytogenetic risk or subtype); however, the trials were usually not powered to detect differences in subgroups. The RCTs were not designed to directly determine which of these factors should guide treatment. The accompanying literature review, while commenting on some characteristics related to treatment, was not sufficient to address this question and no recommendations are being made. Several guidelines on treatment of AML have included sections on patient factors including age, comorbidities, cytogenetic abnormalities and associated risk category, and response to previous treatment. The most recent are the NCCN guideline (10), the Canadian consensus guideline for older patients (24), and the European Society for Medical Oncology (ESMO) guideline for diagnosis, treatment, and follow-up (25). Older but comprehensive management guidelines from Britain (26), Italy (27), and the European LeukemiaNet (2) are also relevant. The reader is referred to these documents for further details. Some of this information may arise from studies that are currently ongoing.