Acute Myeloid Leukemia (AML) Treatment Regimens

Clinical Trials: The National Comprehensive Cancer Network recommends cancer patient participation in clinical trials as the gold standard for treatment.

Cancer therapy selection, dosing, administration, and the management of related adverse events can be a complex process that should be handled by an experienced healthcare team. Clinicians must choose and verify treatment options based on the individual patient; drug dose modifications and supportive care interventions should be administered accordingly. The cancer treatment regimens below may include both U.S. Food and Drug Administration-approved and unapproved indications/regimens. These regimens are only provided to supplement the latest treatment strategies.

These Guidelines are a work in progress that may be refined as often as new significant data becomes available. The NCCN Guidelines® are a consensus statement of its authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult any NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The NCCN makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

▶Induction Therapy[1]

Note: All recommendations are Category 2A unless otherwise indicated. The NCCN believes the best option for any patient with cancer is in a clinical trial and strongly encourages this option for all patients.

PATIENT CRITERIA	REGIMEN AND DOSING
Age <60 years[2-8]	**Days 1–3:** An anthracycline (daunorubicin 60–90mg/m^2 IV **OR** idarubicin 12mg/m^2) **Days 1–7:** Cytarabine 100–200mg/m^2 continuous IV (Category 1). **OR** **Days 1–3:** Daunorubicin 60mg/m^2 IV **Days 1–7:** Cytarabine 200mg/m^2 continuous IV **Days 1–5:** Cladribine 5 mg/m^2. **OR** **Days 1–3:** An anthracycline (daunorubicin 60mg/m^2 IV **OR** idarubicin 12mg/m^2 for 1 cycle) **Days 1–6:** High-dose cytarabine 2g/m^2 IV every 12 hours **OR** **Days 1–4:** High-dose cytarabine 3g/m^2 IV every 12 hours (Category 1 for patients ≤45 years, category 2B for other age groups). **OR** **Days 1–3:** Daunorubicin 60mg/m^2 IV **Days 1–7:** Cytarabine 200mg/m^2 continuous IV every 12 hours **Days 8–21:** Midostaurin 50mg orally every 12 hours.[a] **OR** **Days 1, 3, 5:** Dual-drug liposomal encapsulation of cytarabine 100mg/m^2 + daunorubicin 44mg/m^2 IV over 90 minutes (Category 2B).[b] **OR** **Days 1, 4, 7:** Daunorubicin 60mg/m^2 + gemtuzumab ozogamicin 3mg/m^2 (up to one 4.5 mg vial) **Days 1–7:** Cytarabine 200mg/m^2 continuous IV **OR** **Days 1–7:** SC granulocyte-colony stimulating factor (G-CSF) **Days 2–6:** Fludarabine 30mg/m^2 plus high-dose cytarabine 2g/m^2 over 4 hours after starting fludarabine on days 2–6 **Days 4–6:** Idarubicin 8mg/m^2 IV (Category 2B).
Age ≥60 years[6-10] **De novo AML without unfavorable cytogenetics or molecular markers; no antecedent hematologic disorder; and no therapy-related AML**	**Days 1–3:** An anthracycline (daunorubicin 60–90mg/m^2 IV **OR** idarubicin 12mg/m^2 IV **OR** mitoxantrone 12mg/m^2 IV) **Days 1–7:** Cytarabine 100–200mg/m^2 continuous IV. **OR** **Days 1–3:** Daunorubicin 60mg/m^2 IV **Days 1–7:** Cytarabine 200mg/m^2 continuous IV **Days 8–21:** Midostaurin 50mg orally every 12 hours.[a] **OR** **Days 1, 4, 7:** Daunorubicin 60mg/m^2 + gemtuzumab ozogamicin 3mg/m^2 (up to one 4.5 mg vial) **Days 1–7:** Cytarabine 200mg/m^2 continuous IV (for CD33-positive AML).
Age ≥60 years[6,7,9,10] **Unfavorable cytogenetics or molecular markers; antecedent hematologic disorder; therapy-related AML**	**Lower-intensity therapy** **Days 1–7:** 5-azacytidine 75mg/m^2 IV every 28 days **OR** **Days 1–5:** Decitabine 20mg/m^2 IV for a 4-week cycle. **OR** **Days 1–3:** An anthracycline (daunorubicin 60–90mg/m^2 IV **OR** idarubicin 12mg/m^2 IV **OR** mitoxantrone 12mg/m^2 IV) **Days 1–7:** Cytarabine 100–200mg/m^2 continuous IV. **OR** **Days 1–3:** Daunorubicin 60mg/m^2 IV **Days 1–7:** Cytarabine 200mg/m^2 continuous IV **Days 8–21:** Midostaurin 50mg orally every 12 hours.[a] **OR** **Days 1, 3, 5:** Dual-drug liposomal encapsulation of cytarabine 100mg/m^2 + daunorubicin 44mg/m^2 IV over 90 minutes (Category 1).[b] Clofarabine-based regimens (Category 3).

continued

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▶Induction Therapy[1] (continued)

PATIENT CRITERIA	REGIMEN AND DOSING
Age ≥60 years[11-15] **Not a candidate for intensive therapy or declines intensive therapy**	**Lower-intensity therapy** **Days 1–10:** Cytarabine 20mg SC twice daily. **OR** **Days 1–7:** 5-azacytidine 75mg/m^2 IV every 28 days (preferred). **OR** **Days 1–5:** Decitabine 20mg/m^2 IV every 28 days (preferred). **OR** **Day 1:** Gemtuzumab ozogamicin 6mg/m^2 IV **Day 8:** Gemtuzumab ozogamicin 3mg/m^2 IV (CD-33 positive). **OR** Enasidenib 100mg orally once daily (IDH-2 mutated AML). **OR** Best supportive care (hydroxyurea, transfusion support).

▶Post-Remission Therapy[1]

Age <60 years[12,13] **Core binding factor cytogenetic translocations without *KIT* mutation or favorable-risk molecular abnormalities**	**Days 1, 3, and 5:** High-dose cytarabine 3g/m^2 IV over 3 hours every 12 hours for 3–4 cycles (Category 1) **OR** **Days 1–3:** High-dose cytarabine 3g/m^2 IV over 3 hours every 12 hours for 3–4 cycles. **OR** **Days 1–4:** Cytarabine 1g/m^2 every 12 hours **Day 1:** Gemtuzumab ozogamicin 3mg/m^2 (up to 4.5mg vial) for 2 cycles **Day 1 (Cycle 1) or Days 1–2 (Cycle 2):** Daunorubicin 60mg/m^2 IV (For CD33-positive AML).
Age <60 years **Intermediate-risk and/or molecular abnormalities**	Matched sibling or alternative donor HCT. **OR** **Days 1, 3, 5, OR Days 1–3:** High-dose cytarabine 1.5–3g/m^2 IV over 3 hours every 12 hours for 3–4 cycles. **OR** **Days 1, 3, 5, OR Days 1–3:** High-dose cytarabine 1.5–3g/m^2 IV over 3 hours every 12 hours **Days 8–21:** Midostaurin 50mg orally every 12 hours.[a] **OR** **Days 1–4:** Cytarabine 1g/m^2 every 12 hours **Day 1 (Cycle 1) or Days 1–2 (Cycle 2):** Daunorubicin 60mg/m^2 IV **Day 1:** Gemtuzumab ozogamicin 3mg/m^2 (up to one 4.5mg vial) for 2 cycles (for CD33-positive AML).
Age <60 years **Treatment-related disease other than CBF and/or poor-risk cytogenetics and/or molecular abnormalities**	Matched sibling or alternative donor HCT. **OR** **Days 1, 3, and 5 OR Days 1–3:** High-dose cytarabine 1.5–3g/m^2 IV over 3 hours every 12 hours for 3–4 cycles. **OR** **Days 1, 3, and 5 OR Days 1–3:** High-dose cytarabine 1.5–3g/m^2 IV over 3 hours every 12 hours. **Days 8–21:** Midostaurin 50mg orally every 12 hours.[a] **OR** **Days 1 and 3:** Dual-drug liposomal encapsulation of cytarabine 65mg/m^2 + daunorubicin 29mg/m^2 IV over 90 minutes (Category 2B).[b]
Age ≥60 years **Complete Response After Previous Intensive Therapy**	Reduced-intensity HCT. **OR** Cytarabine 100–200mg/m^2 IV for 5–7 days for 1–2 cycles ± anthracycline (idarubicin or daunorubicin). **OR** Cytarabine 1–1.5g/m^2 IV for 4–6 doses for 1–2 cycles for patients with good performance status, normal renal function, better-risk or normal karyotype with favorable molecular markers. **OR** **Days 1, 3, and 5:** Cytarabine 1–1.5g/m^2 over 3 hours every 12 hours **Days 8–21:** Midostaurin 50mg orally every 12 hours.[a] **OR** **Days 1 and 3:** Dual-drug liposomal encapsulation of cytarabine 65mg/m^2 + daunorubicin 29mg/m^2 IV over 90 minutes.[b] **OR** **Days 1–4:** Cytarabine 1000mg/m^2 IV every 12 hours **Day 1 (Cycle 1) OR Days 1–2 (Cycle 2):** Daunorubicin 60mg/m^2 IV **Day 1:** Gemtuzumab ozogamicin 3mg/m^2 (up to one 4.5mg vial) for 2 cycles (for CD33-positive AML). **OR** Maintenance therapy with hypomethylating regimen (5-azacytidine, decitabine) every 4–6 weeks until progression. **OR** Observation.

continued

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▶Post-Remission Therapy[1] (continued)

PATIENT CRITERIA	REGIMEN AND DOSING
Age ≥60 years **Induction Failure After Previous Intensive Therapy**	Allogeneic HCT (preferably in clinical trial). **OR** Best supportive care.
Age ≥60 years **Response After Previous Lower Intensity Therapy**	Reduced-intensity HCT. **OR** Continue hypomethylating regimens (5-azacytidine, decitabine) every 4–6 weeks until progression. **OR** **Day 1:** Gemtuzumab ozogamicin 2mg/m^2 every 4 weeks up to 8 continuation courses (CD33-positive AML). **OR** Continue enasidenib until progression (IDH-2 mutated AML).
Age ≥60 years **No Response or Progression After Previous Lower Intensity Therapy**	Best supportive care.

▶Therapy for Relapse or Refractory Disease[1]

Age <60 years **Early Relapse (<12 months)**	Chemotherapy* followed by matched sibling or alternative donor HCT.
Age <60 years **Late Relapse (≥12 months)**	Chemotherapy* followed by matched sibling or alternative donor HCT. **OR** Repeat initial successful induction regimen.
Age ≥60 years **Early Relapse (<12 months)**	Chemotherapy* followed by matched sibling or alternative donor HCT. **OR** Best supportive care.
Age ≥60 years **Late Relapse (≥12 months)**	Repeat initial successful induction regimen. **OR** Chemotherapy* followed by matched sibling or alternative donor HCT. **OR** Best supportive care.
***Chemotherapy Options**[8-10, 14-19, 23, 24]	**Aggressive therapy for appropriate patients:** **Days 1–5:** Cladribine 5mg/m^2 IV **Days 1–5:** Cytarabine 2g/m^2 IV **Days 0–5:** G-CSF 300mcg SC, ± **Days 1–3:** Mitoxantrone 10mg/m^2 IV **OR** idarubicin 10mg/m^2 IV. **OR** High-dose cytarabine (if not previously used in treatment) ± anthracycline. **OR** **Days 1–5:** Fludarabine 30mg/m^2 IV over 0.5 hours **Days 1–5:** Cytarabine 2g/m^2 IV over 4 hours **Days 0 to polymorphonuclear recovery (>0.5 x 10^9/L):** G-CSF 5mcg/kg or 300mcg/m^2 (G-CSF may also start on Day +6 until engraftment) ± **Days 1–3:** Idarubicin 10mg/m^2 IV. **OR** **Days 1–6:** Etoposide 80mg/m^2 IV over 1 hour + cytarabine 1g/m^2 IV over 6 hours ± mitoxantrone 6mg/m^2 IV bolus. **OR** **Days 1–5:** Clofarabine 22.5mg/m^2–25mg/m^2 IV ± **Days 2–6:** Cytarabine 0.75g/m^2–2g/m^2 IV **Days 0 to neutrophil recovery:** G-CSF 5mcg/kg/day ± **Days 1–3:** Idarubicin 6-8 mg/m^2 IV. **Less aggressive therapy:** Hypomethylating agents (5-azacytidine or decitabine). **OR** Low-dose cytarabine (Category 2B). **Therapy for patients with FLT3-ITD disease:** **Days 1–7:** 5-azacytidine 75mg/m^2 IV + sorafenib 400 mg orally twice daily continuously. **OR** Decitabine + sorafenib. **Therapy for patients with IDH-2 disease** Enasidenib 100mg orally daily. **Therapy for CD33-positive disease** **Days 1, 4, 7:** Gemtuzumuab ozogamicin 3mg/m^2 IV over 2 hours.

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[a] This regimen is for FLT3 mutation-positive AML (both ITD and TKD) mutations. While midostaurin was not FDA approved for maintenance therapy, the study was designed for consolidation and maintenance midostaurin for a total of 12 months.

[b] For cytotoxic therapy-related AML other than core binding factor [CBF]/APL, or patients with antecedent MDS/CMML, or cytogenetic changes that are consistent with MDS

References

1. NCCN Clinical Practice Guidelines in Oncology™. Acute Myeloid Leukemia. v1.2018. Available at: http://www.nccn.org/professionals/physician_gls/pdf/aml.pdf. Accessed March 29, 2018.
2. Fernandez HF, Sun Z, Yao X, et al. Anthracycline dose intensification in acute myeloid leukemia. *N Engl J Med.* 2009;361(13): 1249–1259.
3. Kern W, Estey EH. High-dose cytosine arabinoside in the treatment of acute myeloid leukemia review of three randomized trials. *Cancer*. 2006;107(1): 116–124.
4. Weick JK, Kopecky KJ, Appelbaum FR, et al. A randomized investigation of high-dose versus standard-dose cytosine arabinoside with daunorubicin in patients with previously untreated acute myeloid leukemia: a Southwest Oncology Group study. *Blood.* 1996:88(8):2841–2851.
5. Bishop JF, Matthews JP, Young GA, et al. A randomized study of high-dose cytarabine in induction in acute myeloid leukemia. *Blood.* 1996;87(5):1710–1717.
6. Lancet JE, Uy GL, Cortes JE, et al. Final results of a phase III randomized trial of CPX-351 versus 7+3 in older patients with newly diagnosed high risk (secondary) AML. *J Clin Oncol.* 2016;34(suppl):abstract 7000.
7. Castaigne S, Pautas C, Terre C, et al. Effect of gemtuzumab ozogamicin on survival of adult patients with de-novo acute myeloid leukaemia (ALFA-0701): a randomised, open label, phase 3 study. *Lancet.* 2012;379:1508-1516.
8. Burnett AK, Hills RK, Milligan D, et al. Identification of patients with acute myeloblastic leukemia who benefit from the addition of gemtuzumab ozogamicin: results of the MRC AML15 trial. *J Clin Oncol.* 2011;29:369-377.
9. Krug U, Röllig C, Koschmieder A, et al. Complete remission and early death after intensive chemotherapy in patients aged 60 years or older with acute myeloid leukaemia: a web-based application for prediction of outcomes. *Lancet.* 2010; 376(9757):2000–2008.
10. Löwenberg B, Ossenkoppele GJ, van Putten W, et al. High-dose daunorubicin in older patients with acute myeloid leukemia. *N Engl J Med.* 2009;361(13): 1235–1248.
11. Burnett AK, Milligan D, Prentice AG, et al. A comparison of low-dose cytarabine and hydroxyurea with or without all-trans retinoic acid for acute myeloid leukemia and high-risk myelodysplastic syndrome in patients not considered fit for intensive treatment. *Cancer.* 2007;109(6):1114–1124.
12. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. *Lancet Oncol.* 2009;10(3):223–232.
13. Cashen AF, Schiller GJ, O'Donnell MR, DiPersio JF. Multicenter, phase II study of decitabine for the first-line treatment of older patients with acute myeloid leukemia. *J Clin Oncol.* 2010;28(4):556–561
14. Kantarjian HM, Erba HP, Claxton D, et al. Phase II study of clofarabine monotherapy in previously untreated older adults with acute myeloid leukemia and unfavorable prognostic factors. *J Clin Oncol.* 2010;28(4):549–555.
15. Stein EM, DiNardo CD, Altman JK, et al. Safety and efficacy of AG-221, a potent inhibitor of mutant IDH2 that promotes differentiation of myeloid cells in patients with advanced hematologic malignancies: results of a phase 1/2 trial. *Blood.* 2015. 2015:126(23):323
16. Mayer RJ, Davis RB, Schiffer CA, 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.
17. Jaramillo S, Benner A, Krauter J, et al. Condensed versus standard schedule of high-dose cytarabine consolidation therapy with pegfilgrastim growth factor support in acute myeloid leukemia. *Blood Cancer J.* 2017;7:e564,
18. Löwenberg B, Pabst T, Vellenga E, et al; Dutch-Belgian Cooperative Trial Group for Hemato-Oncology (HOVON) and Swiss Group for Clinical Cancer Research (SAKK) Collaborative Group. Cytarabine dose for acute myeloid leukemia. *N Engl J Med.* 2011;364(11):1027–1036.
19. Wierzbowska A, Robak T, Pluta A, et al; Polish Adult Leukemia Group. Cladribine combined with high doses of arabinoside cytosine, mitoxantrone, and G-CSF (CLAG-M) is a highly effective salvage regimen in patients with refractory and relapsed acute myeloid leukemia of the poor risk: a final report of the Polish Adult Leukemia Group. *Eur J Haematol.* 2008;80(2):115-126.
20. Fridle C, Medinger M, Wilk MC, et al. Cladribine, cytarabine and idarubicin (CLA-Ida) salvage chemotherapy in relapsed acute myeloid leukemia (AML). *Leuk Lymphoma.* 2017;58(5):1068–1075.
21. Martin MG, Welch JS, Augustin K, et al. Cladribine in the treatment of acute myeloid leukemia: a single-institution experience. *Clin Lymphoma Myeloma.* 2009;9(4):298–301.
22. Montillo M, Mirto S, Petti MC, et al. Fludarabine, cytarabine, and G-CSF (FLAG) for the treatment of poor risk acute myeloid leukemia. *Am J Hematol.* 1998;58(2): 105–109.
23. Parker JE, Pagliuca A, Mijovic A, et al. Fludarabine, cytarabine, G-CSF and idarubicin (FLAG-IDA) for the treatment of poor-risk myelodysplastic syndromes and acute myeloid leukaemia. *Br J Haematol.* 1997;99(4):939–944.
24. Amadori S, Arcese W, Isacchi G, et al. Mitoxantrone, etoposide, and intermediate-dose cytarabine: an effective and tolerable regimen for the treatment of refractory acute myeloid leukemia. *J Clin Oncol.* 1991;9(7):1210–1214.
25. Becker PS, Kantarjian HM, Appelbaum FR, et al. Clofarabine with high dose cytarabine and granulocyte colony-stimulating factor (G-CSF) priming for relapse and refractory acute myeloid leukaemia. *Br J Haematol.* 2011;155(2):182–189.
26. Faderl S, Ferrajoli A, Wierda W, et al. Clofarabine combinations as acute myeloid leukemia salvage therapy. *Cancer.* 2008; 113(8):2090–2096.
27. Ravandi F, Alattar ML, Grunwald MR, et al. Phase 2 study of azacytidine plus sorafenib in patients with acute myeloid leukemia and FLT-3 internal tandem duplication mutation. *Blood.* 2013:121(23):4655–4662.
28. Stein EM, DiNardo CD, Pollyea DA, et al. Enasidenib in mutant IDH2 relapsed or refractory acute myeloid leukemia. *Blood.* 2017;130:722–731.
29. Taksin AL, Legrand O, Raffoux E, et al. High efficacy and safety profile of fractionated doses of Mylotarg as induction therapy in patients with relapsed acute myeloblastic leukemia: a prospective study of the alfa group. *Leukemia.* 2007;21: 66–71.

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