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Release date: January 10, 2021; Expiration date: January 10, 2022

Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to the NCCN Guidelines for Acute Myeloid Leukemia
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Acute Myeloid Leukemia

Disclosure of Relevant Financial Relationships

The NCCN staff listed below discloses no relevant financial relationships:

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To view all of the conflicts of interest for the NCCN Guidelines panel, go to NCCN.org/disclosures/guidelinepanellisting.aspx.

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Acute Myeloid Leukemia, Version 2.2021

Featured Updates to the NCCN Guidelines

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ABSTRACT

The NCCN Guidelines for Acute Myeloid Leukemia (AML) provide recommendations for the diagnosis and treatment of adults with AML based on clinical trials that have led to significant improvements in treatment, or have yielded new information regarding factors with prognostic importance, and are intended to aid physicians with clinical decision-making. These NCCN Guidelines Insights focus on recent select updates to the NCCN Guidelines, including familial genetic alterations in AML, postinduction or postremission treatment strategies in low-risk acute promyelocytic leukemia or favorable-risk AML, principles surrounding the use of venetoclax-based therapies, and considerations for patients who prefer not to receive blood transfusions during treatment.

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Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

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The complete and most recent version of these NCCN Guidelines is available free of charge at NCCN.org.

FAMILIAL GENETIC ALTERATIONS IN AML

- **Patients with a family history of leukemia, or of hematologic cancer or abnormalities, together with the presence of genetic mutations outlined in the table below should be considered for germline testing and genetic counseling. It is strongly recommended that patients with a variant allele frequency (VAF) of 40%–60% of genes associated with a predisposition syndrome be referred for germline testing.**

Name of Syndrome	Causative Gene(s)	Pattern of Inheritance	Characteristic Malignancy	Other Hematopoietic Abnormalities	Other Associated Conditions	Recommended Diagnostic Test
Familial platelet disorder with propensity to myeloid malignancies (OMIM 601399)	*RUNX1*	Autosomal dominant	MDS AML T-cell ALL	Thrombocytopenia Platelet dysfunction		Exon sequencing and gene rearrangement testing for *RUNX1*
Thrombocytopenia 2 (OMIM 188000)	*ANKRD26*	Autosomal dominant	MDS AML	Thrombocytopenia Platelet dysfunction		5'UTR and exon sequencing of *ANKRD26*
Familial AML with mutated CEBPA (OMIM 116897)	*CEBPA*	Autosomal dominant	AML			Exon sequencing and gene rearrangement testing for *CEBPA*
Familial AML with mutated DDX41 (OMIM 608170)	*DDX41*	Autosomal dominant	MDS AML CMML	Monocytosis	Solid tumor predisposition is likely [colon, bladder, stomach, pancreas, breast, and melanoma]	Exon sequencing and gene rearrangement testing for *DDX41*
Thrombocytopenia 5 (OMIM 616216)	*ETV6*	Autosomal dominant	MDS AML CMML B-ALL Myeloma	Thrombocytopenia Platelet dysfunction		Exon sequencing and gene rearrangement testing for *ETV6*
Familial MDS/AML with mutated GATA2 (OMIM 137295)	*GATA2*	Autosomal dominant	MDS AML CMML	Monocytopenia Lymphopenia (NK cell, dendritic cell,B-cell, or CD4+ T-cell)	Sensorineural deafness Immunodeficiency Cutaneous warts Pulmonary alveolar proteinosis MonoMAC syndrome Emberger syndrome	Exon sequencing, intron 5 enhancer region sequencing, and gene rearrangement testing for *GATA2*

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Overview

Acute myeloid leukemia (AML), a heterogeneous hematologic malignancy, is the most common form of acute leukemia among adults and is characterized by the clonal expansion of myeloid blasts in the peripheral blood, bone marrow (BM), and/or other tissues. In the United States, an estimated 19,940 people will be diagnosed with AML in 2020, and 11,180 patients will die of the disease.[1] AML is a disease of older adults, with approximately 54% of patients diagnosed at age ≥65 years,[2] and a median age at diagnosis between 68 and 71 years of age.[1,3] In addition, AML can be subclassified into several categories, including acute promyelocytic leukemia (APL). Recently a new category of myeloid neoplasms with germline disposition was suggested, given that data increasingly demonstrate a link between inherited or de novo germline mutations and myeloid neoplasms, including AML and myelodysplastic syndromes (MDS).[4]

Treatment of AML is divided into initial remission-induction chemotherapy, postremission or consolidation therapy, and, recently, maintenance therapy, using oral azacitidine for patients who are unable to complete intensive curative therapy.[5] Although obtaining a remission is the first step in controlling the disease, it is also important for patients to emerge from the induction phase in a condition that allows them to tolerate subsequent, sometimes more intensive, treatments to achieve durable disease control or cure. Current pretreatment factors, such as age, cytogenetics, and the presence of specific gene mutations, are used to estimate posttreatment risk of relapse.[6–8] Increasing evidence suggests that the evaluation of measurable or minimal residual disease (MRD) is an important part of refining posttreatment risk stratification.[9,10]

In addition, advances in sequencing techniques have broadened our understanding of the molecular basis of AML,[11] which has increased the number of treatment options, including new targeted agents, like venetoclax, and alternative formulations of existing therapies.[6,12] As the use of these novel treatment options increase, it is important to understand and monitor for associated adverse effects to ensure that timely supportive care is implemented. In addition, individualization of treatment and supportive care is an essential component of oncology, and may involve tailoring treatment plans according to a patient's preference.

FAMILIAL GENETIC ALTERATIONS IN AML

Name of Syndrome	Causative Gene(s)	Pattern of Inheritance	Characteristic Malignancy	Other Hematopoietic Abnormalities	Other Associated Conditions	Recommended Diagnostic Test
Familial AML with mutated MBD4	*MBD4*	Autosomal dominant	AML		Colonic polyps	Exon sequencing and gene rearrangement testing for *MBD4*
MECOM-associated syndrome (OMIM 165215 and 616738)	*MECOM/EVI1* complex	Autosomal dominant	MDS AML	Bone marrow failure B-cell deficiency	Radioulnar synostosis Clinodactyly Cardiac malformations Renal malformations Hearing loss	Exon sequencing and gene rearrangement testing for *MECOM/EVI1* complex
Congenital SAMD9/ SAMD9L mutations	*SAMD9* and *SAMD9L*	Autosomal dominant	MDS AML	Pancytopenia	Normophosphatemic familial tumoral calcinosis MIRAGE syndrome Ataxia	Full gene sequencing and gene rearrangement testing for *SAMD9* and *SAMD9L*
Telomere syndromes due to mutation in TERC or TERT (OMIM 127550)	*TERC/TERT*	Autosomal dominant Autosomal recessive (*TERT*)	MDS AML	Macrocytosis Cytopenias Aplastic anemia	Idiopathic pulmonary fibrosis Hepatic cirrhosis Nail dystrophy Oral leukoplakia Skin hypopigmentation Skin hyperpigmentation Premature gray hair Cerebellar hypoplasia Immunodeficiency Developmental delay	Full gene sequencing and gene rearrangement testing for *TERT* and *TERC* Telomere length studies of lymphocyte subsets via FlowFISH SNP array testing (No CLIA-approved testing available)
Myeloid neoplasms with germline predisposition due to duplications of ATG2B and GSKIP	*ATG2B* and *GSKIP*	Autosomal dominant	AML CMML ET	Myelofibrosis		SNP array testing (No CLIA-approved testing available)

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Familial Genetic Alterations in AML

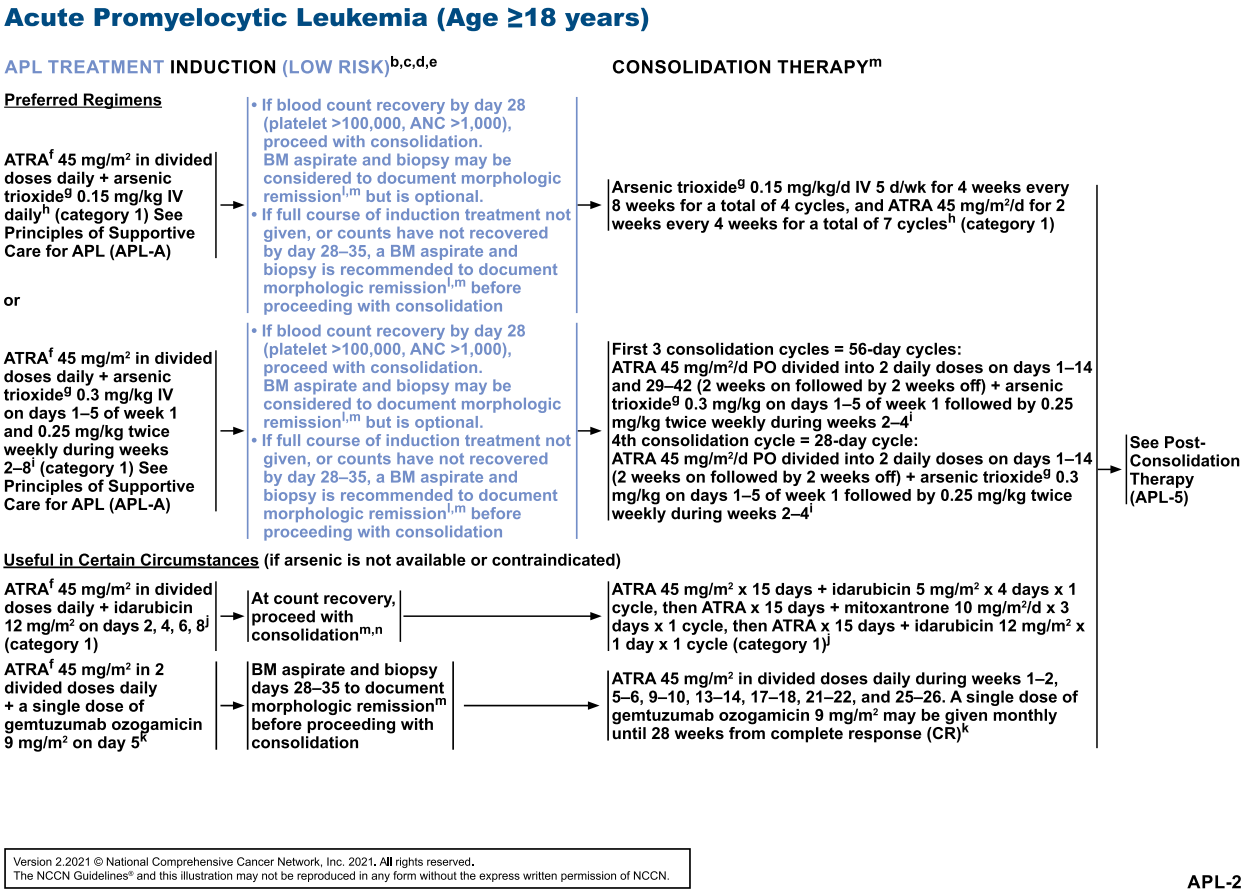
Background

Relative to sporadic cases of AML and MDS, the prevalence of known familial acute leukemia and MDS is considered rare; but with increasing recognition of germline mutations associated with predisposition to developing AML/MDS, identifying these syndromes is important for optimal management of patients and their relatives.[13–16] Evaluation for an underlying familial syndrome in a patient with acute leukemia or MDS should involve a screening history, focused physical examination, and diagnostic genetic testing.[13,17] In particular, the screening evaluation should determine whether the patient has a family history of hematologic malignancies (including AML, acute lymphoblastic leukemia [ALL], or aplastic leukemia) or unexplained leukopenia, anemia (eg, aplastic anemia, macrocytic anemia), and/or thrombocytopenia within 2 generations.[13,14,18,19] In addition, other guidelines recommend that the screening evaluation should determine whether the patient has signs or symptoms indicative of a hereditary condition (including Li Fraumeni syndrome) that predisposes them to developing myeloid neoplasms.[20]

Familial AML with mutated *CEBPA* is one of the most common inherited syndromes associated with AML.[13,21,22] Several reports have noted that all individuals who carry this germline mutation developed AML between 2 and 59 years of age.[13,21,23,24] Other familial AML syndromes include germline mutations in DDX41,[13,25,26] which are relatively common, and germline mutations in *MBD4*,[27] which are rare; syndromes with platelet abnormalities, including familial platelet disorder with mutated *RUNX1*[13,17,28]; or syndromes associated with organ system manifestations, including familial AML/MDS with mutated *GATA2*.[13,17]

NCCN Recommendations

Based on these emerging data, the NCCN AML Panel recommends that patients with a family history of leukemia, or of other hematologic cancers or abnormalities, should be evaluated for an inherited predisposition syndrome (see AML-A 2 and 3 of 3, pages 18 and above, respectively). The panel also strongly recommends that patients with a variant allele frequency (VAF) of 40% to 60% of genes associated with a predisposition



APL-2

syndrome be referred for germline testing. However, there is no consensus on optimal management of individuals diagnosed with familial acute leukemia or MDS, so management must be individualized.[13,17]

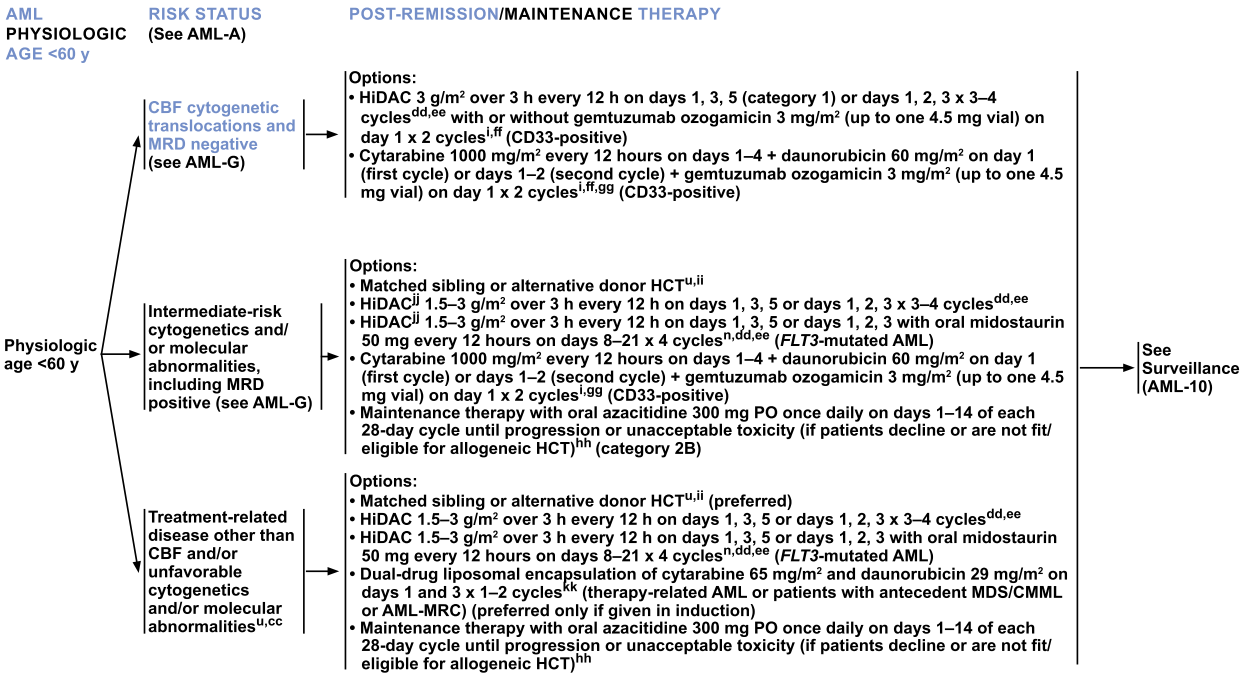
Management of Low-Risk APL: Is a Postinduction BM Needed?

Background

In the previous version of the NCCN Guidelines for AML, patients with low-risk APL who were induced with all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) were recommended to undergo a BM aspirate and biopsy to document morphologic remission at day 28 to 35, before proceeding with consolidation. During this update, the panel discussed whether a BM aspirate after induction should be optional in patients with low-risk APL, given high complete remission (CR) rates observed in this subgroup.[29–31]

In several studies focused on the management of newly diagnosed low-risk APL, after induction with ATRA and ATO-containing regimens a BM aspirate was performed to document whether hematologic remission was achieved, although the time frame to achieving CR can vary.[29–33] In a study by Estey et al[30] among patients with low-risk APL who were treated with ATRA and ATO, weekly BM assessments were performed beginning 25 to 28 days after induction. If the marrow showed <5% blasts and no abnormal promyelocytes, treatment was withheld until CR.

In a phase III randomized trial from the Italian-German Cooperative Group, induction with ATRA + ATO was compared with the AIDA regimen (ATRA + idarubicin) in patients with newly diagnosed, low-, or intermediate-risk APL (n=162).[31] Patients in arm A received ATRA + ATO daily until CR or for a maximum of 60 days, then ATO 5 days per week for 4 weeks every 8 weeks for a total of 4 courses, and ATRA daily for 2 weeks every 4 weeks for a total of 7 courses. Patients in arm B received standard AIDA induction until CR or for a maximum of 60 days, followed by consolidation with 3 cycles of anthracycline-based consolidation combined with ATRA and then maintenance comprising low-dose chemotherapy and ATRA.[34] In both arms, if CR was not achieved



AML-4

by day 60, the patients were taken off study. Among evaluable patients (n=156), CR rates were not different between arms A and B (100% vs 95%). After a median follow-up of 34.4 months, the 2-year event-free survival (EFS) rate was significantly higher in arm A compared with arm B (97% vs 86%; $P<.001$ for noninferiority; $P=.02$ for superiority). The 2-year overall survival (OS) probability was also significantly higher in arm A compared with arm B (99% vs 91%; $P=.02$).[31]

In the randomized phase III AML17 trial, ATRA + ATO was also compared with AIDA in a cohort of patients with APL and without cardiac/pulmonary comorbidities (n=235).[29] ATRA was given to both groups until remission or day 60, after which patients were treated 2 weeks on, then 2 weeks off.[29] The AIDA group received 4 cycles of consolidation consisting of idarubicin and mitoxantrone.[29] The ATRA + ATO consolidation treatment entailed ATO on days 1 through 5 in the first week, twice weekly in weeks 2 through 8 in course 1, and then twice weekly in weeks 2 through 4 during courses 2 through 5. High-risk patients could receive an initial dose of gemtuzumab ozogamicin (GO) at 6 mg/m² for cytoreduction. Comparison between the ATRA + ATO group and the AIDA group showed a higher 4-year EFS (91% vs 70%; $P=.002$) and lower 4-year cumulative incidence of morphologic relapse (1% vs 18%; $P=.0007$) for ATRA + ATO compared with AIDA, although no statistically significant difference in 4-year survival was seen (93% vs 89%; $P=.25$).[29]

NCCN Recommendations

If a patient is cytopenic after induction, one reason for assessing the BM after induction is to differentiate BM myelosuppression from persistent disease. Nonetheless, some panel members questioned the utility of a BM biopsy in this context if the peripheral blood counts have recovered to normal. Based on these data and discussion, during this update the panel decided to revise the guidelines to clarify that if a patient is cytopenic on days 28 through 35, BM biopsy and aspirate are recommended to document blast clearance and to assess whether the marrow is suppressed, and to determine whether ATRA and ATO should be held to allow count recovery (see APL-2, opposite page). If, however, blood counts have recovered by this time point, a BM biopsy may be considered to document remission but is optional (see APL-2, opposite page).

PRINCIPLES OF VENETOCLAX USE WITH HMA OR LDAC-BASED TREATMENT (1 OF 2)

General
- The maximum number of cycles for these regimens is unknown, and treatment may continue as long as tolerated and effective. As data become available, additional insight and guidance about the recommended length of treatment will be provided.
- Reduction in duration of HMA and LDAC or venetoclax treatment can be considered, particularly when there are delays in count recovery.[1]
- Refer to prescribing information and consult with a pharmacist for potential drug interactions (eg, CYP3A4 or CYP2D6 inhibitors).
- The addition of a third agent is not recommended to the combinations described in this section outside the context of a clinical trial.

Therapy for Newly Diagnosed Patients[2]
- Prior to Therapy
  - Try to achieve WBC count of <25,000/mcL with hydroxyurea/leukapheresis if necessary
  - Administer both therapies concomitantly
  - If antifungal prophylaxis is indicated, reduce venetoclax dose accordingly
- First Cycle Considerations
  - Tumor lysis syndrome (TLS) monitoring:
    - In-patient treatment is strongly recommended during first cycle of treatment, especially through dose escalation[3]
    - Intrapatient dose escalation for venetoclax with HMA is 100 mg, 200 mg, and 400 mg daily on days 1–3; intrapatient dose escalation for venetoclax with LDAC target dose is 100 mg, 200 mg, 400 mg, and 600 mg daily on days 1–4
    - Recommend treatment with allopurinol or other uric acid lowering agent until no further risk of TLS
    - Monitor blood chemistries every 6 hours after initiation; continue monitoring until no further risk of TLS
    - Aggressively monitor and manage electrolyte imbalances
  - Continue treatment regardless of cytopenias; transfuse as needed and no growth factors until treatment cycle is complete
  - BM biopsy for response assessment on days 21–28[4]
    - If no morphologic remission but evidence of efficacy exists, proceed with a second cycle without therapeutic interruption with the goal of achieving morphologic remission, and repeat BM biopsy on days 21–28 of this cycle
  - If blasts <5%, hold both therapies and consider the following measures:
    - Administer growth factor support if indicated
    - Monitor blood counts for up to a 14-day period
      - If counts have recovered to a clinically significant threshold (ideally to CR or CRi status) resume the next cycle
      - If counts have not recovered to a clinically significant threshold, consider repeating the BM exam. If morphologic remission is ongoing, can continue to hold therapy for count recovery or start the second cycle with adjustment in the dose or schedule of the HMA/LDAC and/or venetoclax.

[1] Recommend referral to tertiary care center/AMC if need to consider discontinuation of any agent, or to continue maintenance on single-agent venetoclax.
[2] Jonas BA, Pollyea DA. How we use venetoclax with hypomethylating agents for the treatment of newly diagnosed patients with acute myeloid leukemia. Leukemia 2019;33:2795-2804.
[3] Patients may need hospitalization beyond first cycle, based on medical circumstances. Treatment in outpatient setting may be considered per institutional practice or treatment preference.
[4] Combination of venetoclax + decitabine may favor an earlier assessment at day 21 (if blasts are reduced, but no morphologic remission).

Continued

Postremission Therapy for CBF-AML: Consideration of *KIT* Versus MRD

Background

After response to induction chemotherapy, postremission therapy is based on risk status defined by cytogenetics and molecular abnormalities in patients with AML aged <60 years. In the previous version of the NCCN Guidelines for AML, for patients with favorable-risk features and core-binding factor AML (CBF-AML) without *KIT* mutations, postremission treatment recommendations included participation in a clinical trial and intermediate- or high-dose cytarabine (iDAC or HiDAC, respectively) ± GO.[35]

In some studies in which patients with CBF-AML received postremission therapy with HiDAC, the presence of *KIT* mutations resulted in poorer outcomes, particularly in patients with t(8;21).[36,37] One multicenter study that enrolled patients with CBF-AML (n=67) into intensive chemotherapy protocols that involved HiDAC postremission therapy[36] showed that at 24 months, a *KIT* mutation in the tyrosine kinase domain (TKD) at codon 816 (TKD^{816}) in patients with t(8;21) was associated with a significantly higher incidence of relapse (90% vs 35.3%; *P*=.002) and lower OS (25% vs 76.5%; *P*=.006) compared with patients with wild-type *KIT*.[36] In patients with CBF-AML with inv(16), TKD^{816} did not result in a significant difference in relapse incidence and OS.[36] The prognostic influence of TKD^{816} and other mutations in exon 17 (mut*KIT17*) versus other recurrent *KIT* mutations in CBF-AML, such as exon 8 (mut*KIT8*), have been investigated.[37,38]

In an analysis of adult patients aged <60 years with CBF-AML treated with intensive chemotherapy on CALGB trials (n=110), *KIT* mutations (mut*KIT17* and mut*KIT8*) among patients with inv(16) were associated with a higher cumulative incidence of relapse at 5 years (56% vs 29%; *P*=.05) and a decreased 5-year OS rate (48% vs 68%) compared with those with wild-type *KIT*; in multivariate analysis, the presence of *KIT* mutations remained a significant predictor of decreased OS in the subgroup with inv(16). In patients with t(8;21), *KIT* mutations were associated with a higher incidence of relapse at 5 years (70% vs 36%; *P*=.017), but no difference was observed in 5-year OS (42% vs 48%).[37] The CALGB trial also included 4 courses of monthly maintenance chemotherapy with daunorubicin and subcutaneous cytarabine after the consolidation phase; however, only 55% of

PRINCIPLES OF VENETOCLAX USE WITH HMA OR LDAC-BASED TREATMENT (2 OF 2)

Therapy for Newly Diagnosed Patients (Continued)[2]

- Cycle 2 and beyond
  - If no evidence of disease (NED) after cycle 1, repeat BM biopsy at 3- to 6-month intervals, assuming no unexpected changes in blood counts occur.
  - If remission after cycle 1, continue sequential cycles with up to 14-day interruptions between cycles for count recovery and/or growth factor support.
  - If count recovery worsens over time, rule out relapsed disease with repeat BM biopsy. If a morphologic remission is ongoing with worsening blood counts, consider decreasing the dose/schedule of venetoclax and/or HMA/LDAC.
  - Repeat BM biopsy when concerned about relapse.
  - If no morphologic remission after cycle 2, consider enrollment in a clinical trial if available. In the absence of available clinical trials, if the patient has had any response with manageable toxicity, continue therapy as tolerated.

Therapy for Relapsed/Refractory Patients

- Recommend antifungal prophylaxis if indicated.[5]
- Consider the same TLS and intrapatient dose escalation measures as described under "First Cycle Considerations."
- Consider the same recommendations for early BM biopsy and cytopenia mitigation plan proposed under "First Cycle Considerations."

[2] Jonas BA, Pollyea DA. How we use venetoclax with hypomethylating agents for the treatment of newly diagnosed patients with acute myeloid leukemia. Leukemia 2019;33:2795-2804.
[5] Aldoss I, Dadwal S, Zhang J, et al. Invasive fungal infections in acute myeloid leukemia treated with venetoclax and hypomethylating agents. Blood Adv 2019;3:4043-4049.

AML-J
2 of 2

patients in CR received maintenance chemotherapy following HiDAC consolidation.[39] Subsequent clinical trials have eliminated this form of maintenance therapy after postremission therapy. However, the impact of *KIT* mutations in CBF-AML is unclear. A meta-analysis of 11 studies examining the effect of *KIT* mutations on CR, OS, and relapse rates in patients with CBF-AML determined that *KIT* mutations did not affect CR rates.[40] In patients with t(8;21) AML, *KIT* mutations were associated with an increased risk of relapse and shorter OS rates compared with patients with inv(16) AML.[40]

Some studies suggest that after induction, relative to *KIT* mutations, MRD may be a more relevant prognostic factor for CBF-AML risk stratification.[6,41–43] In a prospective study, adult patients with CBF-AML (aged 18–60 years; n=198) were randomized to receive a reinforced induction course (arm A) or standard induction course (arm B), followed by 3 HiDAC consolidation courses.[42] Arm A consisted of a first sequence with daunorubicin (60 mg/m^2/d by a 30-minute intravenous infusion) on days 1 and 3 and cytarabine (500 mg/m^2 continuous infusion) from days 1 to 3, followed by a second sequence at day 8 with daunorubicin (35 mg/m^2/d by a 30-minute intravenous infusion) on days 8 and 9, and cytarabine (1,000 mg/m^2 every 12 hours by a 2-hour infusion) on days 8 and 10.[42] Arm B consisted of cytarabine (200 mg/m^2 continuous infusion) for 7 days combined with daunorubicin (60 mg/m^2) for 3 days. In arm B, at day 15 a peripheral blood and BM evaluation was performed followed by a second sequence of chemotherapy in patients who experienced CR.[42] In addition, MRD levels were serially monitored for *RUNX1-RUNX1T1* and *CBFB-MYH11* by real-time quantitative PCR in BM samples before the first, second, and third consolidation courses. In this study, both treatment arms demonstrated similar efficacy. After first consolidation, higher WBC count, *KIT* and/or *FLT3* gene mutations, and a <3-log MRD reduction were associated with a higher specific hazard of relapse, but MRD was the only prognostic factor in multivariate analysis.[42] At 36 months, the cumulative incidence of relapse and relapse-free survival were 22% and 73%, respectively, in patients who achieved 3-log MRD reduction versus 54% ($P<.001$) and 44% ($P<.001$), respectively, in other patients.[42]

GENERAL CONSIDERATIONS AND SUPPORTIVE CARE FOR AML PATIENTS WHO PREFER NOT TO RECEIVE BLOOD TRANSFUSIONS[1-5]

General Supportive Care

- There is no established treatment of AML that does not require the use of blood and blood products for supportive care.
- Discuss goals of care and understanding of complications without transfusion.
- For Jehovah's Witnesses, the United States Branch of the Christian Congregation of Jehovah's Witness has a Hospital Liaison Committee that could provide helpful information about bloodless medicine: https://www.jw.org/en/medical-library/hospital-liaison-committee-hlc-contacts/united-states/
- Clarify acceptance of certain blood products (eg, cryoprecipitate) under certain circumstances; including a discussion if stem cells (donor or autologous) will be acceptable.
- Minimize blood loss (eg, use of pediatric collection tubes).
- Minimize risk of bleeding including consideration for use of oral contraceptive pills or medroxyprogesterone acetate in menstruating women, proton pump inhibitor, aggressive antiemetic prophylaxis and stool softeners to reduce risk of GI bleed, nasal saline sprays to reduce epistaxis, and fall precautions particularly in patients with thrombocytopenia.
- Avoid concomitant medicines or procedures that can increase the risk of bleeding or myelosuppression.
- Consider using vitamin K (to potentially reverse coagulopathy) and aminocaproic acid or tranexamic acid in patients at risk of bleeding (eg, when platelet count drops below 30,000/μL) or for management of bleeding.
- Consider use of aminocaproic acid rinses for oral bleeding or significant mucositis that could result in bleeding.
- Consider using acetaminophen to manage fever.
- Consider iron, folate, and vitamin B12 supplementation. Iron supplementation may be avoided in someone with excess iron levels.
- Consider use of erythropoiesis-stimulation agent (ESA), G-CSF, and thrombopoietin (TPO) mimetics after a thorough discussion of potential risks, benefits, and uncertainties.
- Consider bed rest and supplemental oxygenation in patients with severe anemia.

Disease-Specific Considerations

- Test for actionable mutations and consider use of targeted agents instead of intensive chemotherapy, particularly in a non-curative setting.
- May consider use of less myelosuppressive induction including dose reduction of anthracyclines, and use of non-intensive chemotherapy.[6]
- Consider referring to centers with experience in bloodless autologous transplant.

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AML-D

NCCN Recommendations

Based on these data and discussion, during this update the NCCN AML Panel revised the risk category from "CBF-AML without *KIT* mutation" to "CBF-AML and MRD-negative" to note the emerging significance of MRD in this risk group (see AML-4, page 21). There are insufficient data to evaluate the use of allogeneic hematopoietic cell transplantation (HCT) in first remission for patients with AML who are MRD-negative and have favorable-risk cytogenetics outside of a clinical trial.[44] Data suggest that the response to treatment is similar regardless of whether the favorable-risk cytogenetics are de novo or treatment-related.[44] However, outcomes for patients with t(8;21) and *KIT* mutations may be less favorable than for those with wild-type *KIT* or inv(16) AML with *KIT* mutations. In the Jourdan et al[42] study described earlier, patients with a <3-log MRD reduction of the *RUNX1-RUNX1T1* transcript level between diagnosis and after 2 cycles of consolidation had a higher rate of relapse. The implications of this suggest that patients with favorable-risk cytogenetics who are above this transcript level after 2 cycles of consolidation may require alternative therapies, including allogeneic transplantation or a clinical trial, but optimal timing is not yet established.

Principles Surrounding Use of Venetoclax-Based Therapies

Background

During the 2021 guidelines update, the panel discussed some comments related to venetoclax use in AML treatment, specifically focused on understanding dose adjustments and potential drug interactions. Given the increasing use of venetoclax-based therapies in AML (eg, venetoclax with hypomethylating agents [HMAs] or low-dose cytarabine [LDAC]), and the fact that these therapies may be given for an indefinite duration as long as patients experience response or derive hematologic benefit from the therapies, the panel reviewed the literature and developed guidelines that can inform ways to optimize use of these therapies.

NCCN Recommendations

Based on existing literature and clinical practice, the panel developed a new section in the guidelines to address the use of venetoclax-based therapies (see AML-J 1 and 2 of 2, pages 22 and 23). For patients with newly diagnosed disease, the panel notes that venetoclax with HMA or LDAC should be given concomitantly.

The addition of a third targeted agent to these combinations is not recommended outside the context of a clinical trial. Prior to administering therapy, it is important to achieve a WBC count of <25,000/mcL with hydroxyurea, or leukapheresis if needed.[45] It is worth noting that the data supporting a beneficial role for leukapheresis in this context is limited.[46] In addition, venetoclax is a substrate of CYP3A4, and therefore dose adjustments of venetoclax are recommended when using it concurrently with strong CYP3A4 inhibitors, most commonly the azole class of antifungal agents.[47] Reductions in duration of venetoclax and HMAs or LDAC may be considered in the setting of cytopenias. If during treatment there is a need to discontinue any of the agents or a consideration to continue maintenance on single-agent venetoclax, the panel recommends referral to a tertiary care or academic medical center.

To minimize the development of tumor lysis syndrome (TLS)—which is uncommon in this setting[45]—during the first cycle of treatment, inpatient treatment is strongly recommended, especially through dose escalation. The intrapatient dose escalation for venetoclax with HMA is 100, 200, and 400 mg given daily on days 1 to 3; and the intrapatient dose escalation for venetoclax with LDAC is 100, 200, 400, and 600 mg given daily on days 1 to 4.[45] To minimize and avert further risk of TLS, the panel recommends aggressive monitoring of blood chemistries, monitoring and managing electrolyte imbalances, and treatment with allopurinol or other uric acid–lowering agent.[45]

Venetoclax and HMAs have been shown to induce prolonged cytopenias even after achieving remission, and neutropenia is a dominant treatment-related toxicity associated with this combination of agents.[48] During the first cycle, the panel recommends continuing treatment regardless of cytopenias until a response assessment is made,[47] with aggressive transfusion support and supportive care as needed. The panel also recommends withholding growth factors until after the first cycle response assessment.[45] However, granulocyte colony-stimulating factors (G-CSFs) should be considered for patients with neutropenia who are in morphologic remission but whose counts have not recovered. A BM biopsy is necessary for response assessment on days 21 through 28 of the first cycle,[45] perhaps on the early end of this range for patients who receive the combination of venetoclax + decitabine.

If blasts are <5% during the first cycle, in the setting of cytopenias all treatment should be held and the following measures should be considered: growth factor support, if indicated, and a treatment-free interval for up to 14 days. When counts have recovered to a clinically significant threshold (ideally to CR or CR with incomplete hematologic recovery), the next cycle of treatment can begin.[45] If counts have not recovered to a clinically significant threshold, a repeat BM biopsy should be considered. If morphologic remission is ongoing, therapy can continue to be held or a second cycle can proceed with adjustments to dose or schedule of venetoclax and HMA or LDAC.[45]

During the second and subsequent cycles of treatment, if remission was observed after the first cycle, sequential cycles should continue with up to 14-day interruptions between cycles for count recovery and/or growth factor support.[45] If there is no evidence of disease after the first cycle, and assuming no unexpected changes in blood counts occur, the BM biopsy can be repeated at 3- to 6-month intervals, or as needed based on clinical suspicion for relapse, depending on the goals of the patient. If count recovery worsens over time, relapsed disease should be ruled out with a repeat BM biopsy.[45] If morphologic remission is ongoing with worsening blood counts, decreasing the duration, and/or dose, of venetoclax and/or HMA or LDAC should be considered. However, if there is no morphologic remission after the second cycle, enrollment in a clinical trial should be considered if available. If no clinical trial is available, and patient has had some response with manageable toxicity, therapy may be continued as long as it is tolerated.

If venetoclax and HMA or LDAC are being given to patients with relapsed/refractory AML, the panel recommends antifungal prophylaxis.[48] Other recommendations for TLS, intrapatient dose escalation, BM biopsies, and cytopenia mitigation plans are similar to considerations that have been described.

Considerations for Patients With AML Who Prefer Not to Receive Blood Transfusions

Background

During this update, the AML panel considered a set of comments proposing that guidance should be offered to clinicians with patients who would prefer not to receive blood transfusions as part of their care. There is no established treatment of AML that does not require use of blood and blood products for supportive care, and with limited data, providing guidelines or recommendations for AML management in this context is challenging. However, the panel recognizes that this is a significant issue faced in a narrow spectrum of clinical settings. In this context, the panel reviewed the existing literature and collective experience with this issue and summarized some considerations to guide treatment and supportive care in a new section (see AML-D, opposite page). However, it is important to note that the panel believes that in many cases, good outcomes from these strategies are rare.

NCCN Recommendations

At the outset, it is important to discuss the goals of care with the patient and establish an understanding of the complications that can arise without transfusions. In addition, it will be helpful to ascertain whether the patient will accept certain blood products (eg, cryoprecipitate) and stem cells (either autologous or from another donor source). To mobilize peripheral blood stem cells and/or raise hemoglobin levels prior to peripheral blood stem cell transplantation, some treatment centers have used erythropoietin-stimulating agents, G-CSF, and thrombopoietin mimetics.[49–51] However, before using this strategy, the potential risks, benefits, and uncertainties of using these agents in this context should be thoroughly discussed. Consider referring patients to centers with expertise in bloodless autologous transplant.[50,51] In addition, for patients who are Jehovah's Witnesses and therefore refuse blood transfusions, the United States branch of the Christian Congregation of Jehovah's Witness has Hospital Liaison Committees that may provide helpful information about bloodless medicine.

Regarding treatment options, the panel recommends considering less myelosuppressive induction, including dose reduction of anthracyclines and use of nonintensive chemotherapy.[52–56] Some of these options may include targeted agents guided by testing for actionable mutations rather than intensive chemotherapy, especially in a noncurative setting. However, the panel notes that chemotherapy dose reductions without transfusion support in patients with AML are associated with a lower rate of remission and a high mortality rate due to severe anemia, and are unlikely to result in durable remissions.[55] During treatment, measures should be taken to minimize blood loss and decrease the risk of bleeding, including use of pediatric collection tubes, avoiding concomitant medications or procedures that increase the risk of bleeding or myelosuppression, use of oral contraceptive pills or medroxyprogesterone acetate in menstruating women, or administration of proton pump inhibitors, as indicated.[50,57] Vitamin K may be considered as an adjuvant to improve coagulopathy.[50,57] In patients at risk for bleeding (eg, when platelet counts decrease to <30,000/mcL), aminocaproic or tranexamic acid may be considered to manage bleeding.[50,57] In patients with elemental or vitamin deficiencies, iron, folate, and vitamin B12 supplementation should be considered.[50,57] In patients with severe anemia, bed rest and supplemental oxygenation should be considered.[50,57]

Conclusions

The goal of any therapeutic strategy is to achieve durable CR and minimize treatment-related toxicities. During the 2021 update of the NCCN Guidelines for AML, the panel addressed some of these issues by adding new sections to the guidelines. One section highlights the importance of screening patients and their families for germline mutations that characterize hereditary myeloid malignancy syndromes.[17] Other sections offer recommendations on optimal use of venetoclax-based therapies[45] and considerations for patients who prefer not to receive blood products during care. Regarding risk-stratification, in patients with low-risk APL treated with ATRA + ATO induction therapy, the panel clarified that a BM assessment should be optional if blood counts have recovered by day 28.

Once a patient is in remission, physicians must decide whether to continue treatment with allogeneic HCT to prevent relapse, and relying solely on pretreatment factors may be inadequate.[58] To note the emerging significance of MRD relative to *KIT* mutations in posttreatment risk assessment, the panel also revised the guidelines to state that patients who have CBF-AML and are MRD-negative after induction may proceed to postremission treatment that does not involve allogeneic HCT. Ongoing studies are evaluating the impact of interventions based on MRD,[9] and emerging data will continue to inform the panel's recommendations in the NCCN Guidelines for AML.

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