Acute Myeloid Leukemia

Clinical Practice Guidelines in Oncology

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Overview

In 2010, approximately 12,330 people were diagnosed with and 8950 died of acute myeloid leukemia (AML).1 As the population ages, the incidence of AML, along with myelodysplasia, seems to be rising. Equally disturbing is the increasing incidence of treatment-related myelodysplasia and leukemia in survivors of childhood tumors and young adulthood, such as Hodgkin disease, sarcomas, breast and testicular cancers, and lymphomas. Ionizing radiation and occupational exposure to benzene and petrochemicals are also associated with AML.2

The NCCN AML Panel convenes annually to update guidelines for the diagnosis and treatment of AML in adults. Clinical trials have led to significant improvements in treatment in some areas, primarily

Please Note

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Disclosures for the NCCN Guidelines Panel for Acute Myeloid Leukemia

At the beginning of each NCCN Guidelines panel meeting, panel members disclosed any financial support they have received from industry. Through 2008, this information was published in an aggregate statement in JNCCN and online. Furthering NCCN’s commitment to public transparency, this disclosure process has now been expanded by listing all potential conflicts of interest respective to each individual expert panel member.

Individual disclosures for the NCCN Guidelines for Acute Myeloid Leukemia panel members can be found on page 317. (The most recent version of these guidelines and accompanying disclosures, including levels of compensation, are available on the NCCN Web site at www.NCCN.org.)

These guidelines are also available on the Internet. For the latest update, please visit www.NCCN.org.
in acute promyelocytic leukemia (APL). However, recent large clinical trials have highlighted the need for new, innovative strategies because outcomes for patients, particularly older patients, have not substantially changed in the past 3 decades.

The panel has focused on outlining reasonable treatment options based on recent clinical trials and data from basic science, which may identify new risk factors and treatment approaches. In some areas, panel members have divergent opinions about the relative risks and benefits of various treatment options. Therefore, these guidelines attempt to provide a rationale for the inclusion of several treatment options in some categories.

**Initial Evaluation**

Initial evaluation has 2 objectives. The first is to characterize the disease process, including factors such as 1) prior toxic exposure, 2) myelodysplasia, and 3) karyotypic or molecular abnormalities, which may provide prognostic information that could influence responsiveness to chemotherapy and risk of relapse. The second objective focuses on patient-specific factors, including comorbid conditions that may affect an individual’s ability to tolerate chemotherapy. Both disease-specific and individual patient factors are considered in treatment decisions.

Two systems are commonly used by pathologists to define hematopoietic malignancies. The French-American-British (FAB) classification is based on morphology, relying on cytochemical stains, and also...
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**CLASSIFICATION/STAIN ANALYSIS**

**Acute promyelocytic leukemia (APL)**
- See Treatment Induction (facing page)

**Acute myeloid leukemia (AML)**
- See Treatment Induction (page 288)

**Appropriate therapy for acute lymphoblastic leukemia (ALL)**

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**Acute leukemia**

- Acute leukemia or chloroma

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**DIAGNOSIS**

**WORKUP**

<table>
<thead>
<tr>
<th>Acute leukemia</th>
<th><strong>CLASSIFICATION/STAIN ANALYSIS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>November 2010</td>
<td>Immunophenotyping (+) for ≥ 2 myeloid markers and typically (+) for &lt; 2 lymphoid markers or Myeloperoxidase (+) or Nonspecific esterase (+) or Butyrate esterase (+)</td>
</tr>
<tr>
<td>November 2010</td>
<td>Acute promyelocytic leukemia (APL)</td>
</tr>
<tr>
<td>November 2010</td>
<td>Acute myeloid leukemia (AML)</td>
</tr>
<tr>
<td>November 2010</td>
<td>Appropriate therapy for acute lymphoblastic leukemia (ALL)</td>
</tr>
</tbody>
</table>

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**a** The WHO classification defines acute leukemia as ≥ 20% blasts in the marrow or blood. A diagnosis of AML may be made with < 20% blasts in patients with recurrent cytogenetic abnormalities (e.g., t(15;17), t(8;21), t(16;16), inv(16)). Ongoing clinical trials for AML and high-risk MDS may continue to use FAB criteria of ≥ 30% blasts, at least until completion of those trials. AML evolving from MDS (AML-MDS) is often more resistant to cytotoxic chemotherapy than AML, which arises without antecedent hematologic disorder and may have a more indolent course. Some clinical trials designed for high-grade MDS may allow enrollment of patients with AML-MDS.

**b** Young adults may be eligible for pediatric trials with more intensive induction regimens and transplant options. AML patients should preferably be managed at experienced leukemia centers where clinical trials may be more available.

**c** Patients who present with isolated extramedullary disease (chloroma) should be treated with systemic therapy. Local therapy (surgery/RRT) may be used for residual disease.

**d** Samples for both techniques should be taken during initial sampling. Prioritization of these 2 complementary diagnostic procedures is left to the discretion of the pathology departments of the individual institutions. M0 can only be diagnosed through immunophenotyping. The role of immunophenotyping in detecting minimal residual disease is being evaluated.

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**Acute promyelocytic leukemia (APL)**

- See Treatment Induction (facing page)

**Acute myeloid leukemia (AML)**

- See Treatment Induction (page 288)

**Appropriate therapy for acute lymphoblastic leukemia (ALL)**

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**Clinical trials:** NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.
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**Apoptosis**

**Classification**

- **M3 morphology** and (+) for t(15;17) by either cytogenetics or molecular testing; consider possibility of M3 variant

- **M3 morphology** and (+) for t(15;17) by either cytogenetics or molecular testing; consider possibility of M3 variant

- **Not able to tolerate anthracyclines**
  - **ATRA, 45 mg/m² in 2 divided doses daily + arsenic trioxide, 0.15 mg/kg IV daily** until bone marrow remission
  - **Assess marrow morphology at count recovery from start of induction**
  - **Complete response**

- **Able to tolerate anthracyclines**
  - **High-risk (WBC > 10,000/mcL)**
    - **See Treatment Induction (page 284)**
  - **Low-intermediate-risk (WBC ≤ 10,000/mcL)**
    - **See Treatment Induction (page 285)**

- **Arsenic trioxide, 0.15 mg/kg IV daily 5 d/wk every other mo for 4 cycles with ATRA, 45 mg/m² in 2 divided doses daily orally during 2 wk monthly (for a total of 7 cycles).**

**Induction**

- **Primary resistance is rare. Most induction failures are related to bleeding or differentiation syndrome. Treatment options include clinical trial, matched sibling, or alternative donor HSCT.**

- **Several groups have published large trials with excellent outcomes. However, to achieve the expected results, one needs to use the regimen consistently through all components and not mix induction from one with consolidation from another.**

- **Therapy-related APL is treated the same as de novo APL.**

- **In patients with clinical and pathologic features of APL, start ATRA on first suspicion of APL without waiting for genetic confirmation of the diagnosis. Early initiation of ATRA prevents the lethal complication of bleeding. If cytogenetic and molecular testing does not confirm APL, discontinue ATRA and continue treatment as for AML.**

- **Monitor for APL differentiation syndrome and disseminated intravascular coagulation (DIC). See Supportive Care (page 297).**


- **See Arsenic trioxide monitoring, Supportive Care (page 297).**

- **Assessment of molecular remission should not be made before 4-5 wk after induction, and should be made after consolidation. Because premature morphologic and molecular assessment (day 10-14 marrow) can be misleading, a nadir marrow is not recommended. Differentiation of the leukemic promyelocytes usually requires more time. Patients often remain molecularly positive at the end of induction even when the marrow shows morphologic remission.**

- **See Response Criteria for Acute Myeloid Leukemia (page 298).**

- **Primary resistance is rare. Most induction failures are related to bleeding or differentiation syndrome. Treatment options include clinical trial, matched sibling, or alternative donor HSCT.**

**Consolidation Therapy**

**See Post-consolidation Therapy (page 286).**
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#### APL TREATMENT INDUCTION\(h,k\)

**Able to tolerate anthracyclines**

<table>
<thead>
<tr>
<th>High-risk (WBC &gt; 10,000)(h)</th>
<th>(\times 4) d + cytarabine, 200 mg/m(^2) x 7 d(h)</th>
<th>Complete response(o,v)</th>
<th>(\times 7) d(h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ATRA(h), 45 mg/m(^2) + daunorubicin, 50 mg/m(^2)</td>
<td>Assess marrow morphology at start of induction(h)</td>
<td>Arsenic trioxide,(m) 0.15 mg/kg/d x 5 d for 5 wk for 2 cycles, then ATRA, 45 mg/m(^2) x 7 d + daunorubicin, 50 mg/m(^2) x 3 d for 2 cycles(s)</td>
</tr>
<tr>
<td></td>
<td>or ATRA(h), 45 mg/m(^2) + daunorubicin, 60 mg/m(^2) x 3 d + cytarabine, 200 mg/m(^2) x 7 d(h)</td>
<td>Complete response(o,v)</td>
<td>Daunorubicin, 60 mg/m(^2) x 3 d + cytarabine, 200 mg/m(^2) x 7 d for 1 cycle, then cytarabine, 1.5-2 g/m(^2) every 12 h x 5 d(y) + daunorubicin, 45 mg/m(^2) x 3 d for 1 cycle 5 doses of IT chemotherapy(l) (category 1)</td>
</tr>
<tr>
<td></td>
<td>or ATRA(h), 45 mg/m(^2) + idarubicin, 12 mg/m(^2) on days 2, 4, 6, 8(u)</td>
<td>Complete response(o,v)</td>
<td>ATRA, 45 mg/m(^2) x 15 d + idarubicin, 5 mg/m(^2) and cytarabine, 1 g/m(^2) x 4 d for 1 cycle, then ATRA x 15 d + mitoxantrone, 10 mg/m(^2)/d x 5 d for 1 cycle, then ATRA x 15 d + idarubicin, 12 mg/m(^2) x 1 dose + cytarabine, 150 mg/m(^2)/8 h x 4 d for 1 cycle(v)</td>
</tr>
<tr>
<td>or Clinical trial</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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\(h\)Several groups have published large trials with excellent outcomes. However, to achieve the expected results, one needs to use the regimen consistently through all components and not mix induction from one with consolidation from another.

\(k\)Monitor for APL differentiation syndrome and disseminated intravascular coagulation (DIC), see Supportive Care (page 297).

\(m\)See Arsenic trioxide monitoring, Supportive Care (page 297).

\(n\)Assessment of molecular remission should not be made before 4-5 wk after induction, it should be made after consolidation. Because premature morphologic and molecular assessment (day 10-14 marrow) can be misleading, a nadir marrow is not recommended. Differentiation of the leukemic promyelocytes usually requires more time. Patients often remain molecularly positive at the end of induction even when the marrow shows morphologic remission.

\(o\)See Response Criteria for Acute Myeloid Leukemia (page 298).

\(v\)See Post-consolidation Therapy (page 286).

\(u\)For patients with a high WBC (> 10,000/mcl), consider prophylactic dexamethasone to prevent differentiation syndrome.

\(w\)Data suggest that lower doses of ATRA (25 mg/m\(^2\)) may be used in children and young adults.

\(x\)Assessment of molecular remission should not be made before 4-5 wk after induction, it should be made after consolidation. Because premature morphologic and molecular assessment (day 10-14 marrow) can be misleading, a nadir marrow is not recommended. Differentiation of the leukemic promyelocytes usually requires more time. Patients often remain molecularly positive at the end of induction even when the marrow shows morphologic remission.

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\(v\)Induction failure is related to bleeding, differentiation, or infection and not disease progression. See relapse on page 287.

\(w\)All regimens include high cumulative doses of cardiotoxic agents. Cardiac function should be assessed before each anthracycline/mitoxantrone-containing course.

\(x\)Although the original regimen included high-dose cytarabine as second consolidation, some investigators recommend using high-dose cytarabine early for CNS prophylaxis, especially for patients not receiving IT chemotherapy.

\(y\)Dose adjustment of cytarabine may be needed for older patients or patients with renal dysfunction.
### Acute Myeloid Leukemia Version 2:2011

**APL**

**TREATMENT INDUCTION**

Able to tolerate anthracyclines

<table>
<thead>
<tr>
<th>Low-/intermediate- (Int) risk (WBC ≤ 10,000)</th>
<th>ATRA, 45 mg/m² + daunorubicin, 50 mg/m² x 4 days + cytarabine, 200 mg/m² x 7 days⁵,⁶,⁻²</th>
<th>Assess marrow morphology at count recovery from start of induction⁹</th>
<th>Complete response⁰,⁴,⁸,⁹</th>
</tr>
</thead>
<tbody>
<tr>
<td>or</td>
<td>ATRA, 45 mg/m² + daunorubicin, 60 mg/m² x 3 days + cytarabine, 200 mg/m² x 7 days⁵,⁶,⁻² (category 1)</td>
<td>Assess marrow morphology at count recovery from start of induction⁹</td>
<td>Complete response⁰,⁴,⁸,⁹</td>
</tr>
<tr>
<td>or</td>
<td>ATRA, 45 mg/m² + idarubicin, 12 mg/m² on days 2, 4, 6, 8⁶,⁻² (category 1)</td>
<td>Assess marrow morphology at count recovery from start of induction⁹</td>
<td>Complete response⁰,⁴,⁸,⁹</td>
</tr>
<tr>
<td>Clinical trial</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**CONSOLIDATION THERAPY**

| Arsenic trioxide, 0.15 mg/kg/d x 5 d for 5 wk for 2 cycles, then ATRA, 45 mg/m² x 7 d + daunorubicin, 50 mg/m² x 3 d for 2 cycles⁵ |

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⁵Several groups have published large trials with excellent outcomes. However, to achieve the expected results, one needs to use the regimen consistently through all components and not mix induction from one with consolidation from another.

⁶Monitor for APL differentiation syndrome and disseminated intravascular coagulation (DIC), see Supportive Care (page 297).

⁷See Arsenic trioxide monitoring, Supportive Care (page 297).

⁸Assessment of molecular remission should not be made before 4-5 wk after induction, it should be made after consolidation. Because premature morphologic and molecular assessment (day 10-14 marrow) can be misleading, a nadir marrow is not recommended. Differentiation of the leukemic promyelocytes usually requires more time. Patients often remain molecularly positive at the end of induction even when the marrow shows morphologic remission.

⁹See Response Criteria for Acute Myeloid Leukemia (page 298).

¹⁰Data suggest that lower doses of ATRA (25 mg/m²) may be used in young adults.


¹⁴Induction failure is related to bleeding, differentiation, or infection and not disease progression. See relapse on page 287.

¹⁵All regimens include high cumulative doses of cardiotoxic agents. Cardiac function should be assessed before each anthracycline/mitoxantrone-containing course.

¹⁶Dose adjustment of cytarabine may be needed for older patients or patients with renal dysfunction.

¹⁷Patients who have rapidly escalating WBC or other high-risk features during course of induction therapy, see consolidation on page 284.
Polymerase chain reaction (PCR) should be performed on a marrow sample at completion of consolidation to document molecular remission. Subsequent monitoring with PCR can be performed with peripheral blood, although using marrow sample is a more sensitive monitoring technique and may give earlier signs of relapse. Prior practice guidelines have recommended monitoring marrow with PCR every 3 mo for 2 y to detect molecular relapse. The panel continues to endorse this for high-risk patients, those older than 60 y or who had long interruptions during consolidation, or those not able to tolerate maintenance. Clinical experience indicates that risk of relapse in patients with low-risk disease who are in molecular remission at completion of consolidation is low and monitoring may not be necessary outside the setting of a clinical trial. To confirm PCR positivity, a second marrow sample should be tested in 2-4 wk in a reliable laboratory. If molecular relapse is confirmed by a second positive test, intervention should be strongly considered (e.g., arsenic trioxide). If the second test was negative, frequent monitoring (every 3 mo for 2 y) is strongly recommended to confirm that the patient remains PCR-negative. The PCR testing laboratory should indicate level of sensitivity of assay for positivity (most clinical laboratories have a sensitivity level of $10^{-4}$) and testing should be performed in the same laboratory to maintain the same level of sensitivity. Consider consultation with a physician experienced in molecular diagnostics if results are equivocal.

If patient confirmed molecularly positive, treat as relapse (facing page).

The role of maintenance chemotherapy remains unclear, particularly for patients with low-risk disease who experience a molecular remission at the end of consolidation. Most studies showing benefit for maintenance occurred before the use of ATRA for consolidation. Trials are evaluating benefits of maintenance in this group.
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**Notes:**

- **See Arsenic trioxide monitoring, Supportive Care (page 297).**
- **dd** At the end of 2 cycles, if patient is not in molecular remission, consider matched sibling or alternative donor HSCT or clinical trial. Testing is recommended at least 2-3 wk after the completion of arsenic to avoid false-positives.
Patients with favorable karyotypes (inv16, t(8;21), t(16;16)) should be managed at experienced leukemia centers where clinical trials may be available.

Patients with blast counts > 50,000/mcL are at risk for tumor lysis and organ dysfunction secondary to leukostasis. Measures to rapidly reduce the white cell count include apheresis or hydroxyurea. Prompt institution of definitive therapy is essential.

For patients with impaired cardiac function, other regimens that combine amm nonanthracycline (e.g., fludarabine, topotecan) with cytarabine have been published.

The use of high-dose cytarabine for induction outside the setting of a clinical trial is still controversial. Although the remission rates are the same for standard- and high-dose cytarabine, 2 studies have shown more rapid marrow blast clearance after one cycle of high-dose therapy and a disease-free survival advantage for patients < 50 years of age who received the high-dose therapy (category 2B). (Kern W, Estey EH. High-dose cytarabine/arabinoside in the treatment of acute myeloid leukemia: review of three randomized trials. Cancer 2006;107:116-124.) No data are available using more than 60 mg of daunorubicin or 12 mg of idarubicin with high-dose cytarabine.
AML POSTINDUCTION THERAPY
AFTER STANDARD-DOSE CYTARABINE
Age < 60 y

- Follow-up bone marrow 7-10 d after induction completed
  - Significant residual blasts
  - Significant cyto-reduction with low % residual blasts
  - Hypoplasia
  - Await recovery

- High-dose cytarabine or standard-dose cytarabine with idarubicin or daunorubicin
  - or
  - See treatment for Induction failure

POSTREMISSION THERAPY

- Complete response
- See Postremission Therapy (page 291)

- Induction failure
- Clinical trial or Matched sibling or alternative donor HSCT
- or
- High dose cytarabine (if not previously used as treatment for persistent disease at day 15) ± anthracycline (daunorubicin or idarubicin), if clinical trial not available while awaiting identification of a donor or Best supportive care

<table>
<thead>
<tr>
<th>Postinduction Therapy After Standard-Dose Cytarabine</th>
<th>Postremission Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up bone marrow 7-10 d after induction completed</td>
<td>Complete response</td>
</tr>
<tr>
<td>- Significant residual blasts</td>
<td>See Postremission Therapy (page 291)</td>
</tr>
<tr>
<td>- Significant cyto-reduction with low % residual blasts</td>
<td>Induction failure</td>
</tr>
<tr>
<td>- Hypoplasia</td>
<td>Clinical trial or Matched sibling or alternative donor HSCT</td>
</tr>
<tr>
<td></td>
<td>- High dose cytarabine (if not previously used as treatment for persistent disease at day 15) ± anthracycline (daunorubicin or idarubicin), if clinical trial not available while awaiting identification of a donor or Best supportive care</td>
</tr>
</tbody>
</table>

- See Response Criteria for Acute Myeloid Leukemia (page 298).
- See Supportive Care (page 297).
- See Monitoring During Therapy (page 298).

ECOG reported a significant increase in CR rates and OS using daunorubicin, 90 mg/m² x 3 days, versus 45 mg/m² x 3 days in patients < 60 years of age. (Fernandez HF, Sun Z, Yao X, et al. Anthracycline dose intensification in acute myeloid leukemia. N Engl J Med 2009;361:1249-1259.) If residual disease is present on day 12-14, additional daunorubicin dose is 45 mg/m² x 3 days.

If ambiguous, consider repeat bone marrow biopsy in 5-7 d before proceeding with therapy.

Hypoplasia is defined as cellularity < 10%-20% and residual blasts < 5%-10%.

Patients with an increased risk of meningeal involvement (initial WBC > 100,000/mCL or monocytic histology) should be considered for CNS evaluation with a lumbar puncture on experiencing complete response. See Evaluation and Treatment of CNS Leukemia (page 296).
AML POSTINDUCTION THERAPY
AFTER HIGH-DOSE CYTARABINE
Age < 60 y

- Significant residual blasts
  - See treatment for Induction failure
- Significant cytoreduction with low % residual blasts
  - Await recovery
- Hypoplasia
  - Await recovery

Follow-up bone marrow
- 7-10 d after induction completed

Postremission Therapy

- Complete response
  - Marrow to document remission status upon hematologic recovery
  - Clinical trial
    - or
    - Matched sibling or alternative donor HSCT or
    - Best supportive care

- Induction failure
  - Clinical trial or
  - Matched sibling or alternative donor HSCT or
  - 1 to 2 cycles of high-dose cytarabine-based consolidation followed by autologous HSCT or
  - High-dose cytarabine 1.5-3 g/m² over 3 h every 12 h on days 1, 3, 5 x 3-4 cycles (category 1) followed by maintenance therapy (category 2B) or
  - 1 to 2 cycles of high-dose cytarabine-based consolidation followed by autologous HSCT

- Better-risk cytogenetics or molecular abnormalities
  - High-dose cytarabine 1.5-3 g/m² over 3 h every 12 h on days 1, 3, 5 x 3-4 cycles or
  - Clinical trial

- Intermediate-risk cytogenetics or molecular abnormalities
  - Clinical trial or
  - Matched sibling or alternative donor HSCT or
  - 1 to 2 cycles of high-dose cytarabine-based consolidation followed by autologous HSCT if no allogeneic transplant option available or
  - High-dose cytarabine 1.5-3 g/m² over 3 h every 12 h on days 1, 3, 5 x 3-4 cycles or
  - Clinical trial

- Treatment-related disease or poor-risk cytogenetics or molecular abnormalities
  - See Response Criteria for Acute Myeloid Leukemia (page 298).
  - See Supportive Care (page 297).
  - See Monitoring During Therapy (page 298).

Follow-up bone marrow
- 7-10 d after induction completed

- Hypoplasia
  - Defined as cellularity < 10%-20% and residual blasts < 5%-10%.

- Patients with an increased risk of meningeal involvement (initial WBC > 100,000/mcL or monocytic histology) should be considered for CNS evaluation with a lumbar puncture on experiencing complete response. See Evaluation and Treatment of CNS Leukemia (page 296).

See Response Criteria for Acute Myeloid Leukemia (page 298).
See Supportive Care (page 297).
See Monitoring During Therapy (page 298).
Begin alternate donor search (unrelated donor or cord blood) if no appropriate sibling donor is available and patient is a candidate for an allogeneic HSCT.

Mutations are also emerging as a poor-risk feature in the setting of otherwise normal karyotype, and these patients should be considered for clinical trials where available. Controversy exists regarding allogeneic transplant for only mutations in the absence of other poor prognostic features.

Although the original study design incorporated maintenance chemotherapy after a planned 4 cycles of consolidation, only a small fraction of the patients who received high-dose cytarabine also received maintenance therapy. (Mayer RJ, Davis RB, Schiffer CA, et al. Intensive postremission chemotherapy in adults with acute myeloid leukemia. N Engl J Med 1994;331:896-903.)

Although both options -- (1) multiple cycles of dose-intensive consolidation and (2) one cycle of dose-intensive consolidation followed by autologous HSCT -- can produce good survival for patients with favorable cytogenetics, there are significant differences in toxicity. Patient age, comorbid conditions, and issues such as fertility and salvage options should be considered when choosing consolidation.

Clinical trials, when available, are strongly recommended in the treatment of patients with poor prognostic features (e.g., high WBC, 2 cycles of induction needed to produce CR).

Patients may require at least one cycle of high-dose cytarabine consolidation during donor search to maintain remission. Patients may proceed directly to transplant after remission occurs if a donor (sibling or alternative) is available.
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RISK STATUS (See page 296)

POSTREMISSION THERAPY

Better-risk cytogenetics or molecular abnormalities

High-dose cytarabine 1.5-3 g/m² over 3 h every 12 h on days 1, 3, 5 x 3-4 cycles (category 1) followed by maintenance therapy (category 2B) or 1 to 2 cycles of high-dose cytarabine-based consolidation followed by autologous HSCT (category 2B) or Clinical trial

See Surveillance (page 295)

Intermediate-risk cytogenetics or molecular abnormalities

Matched sibling or unrelated donor HSCT or 1 to 2 cycles of high-dose cytarabine-based consolidation followed by autologous HSCT or High-dose cytarabine 1.5-3 g/m² over 3 h every 12 h on days 1, 3, 5 x 3-4 cycles or Clinical trial

See Surveillance (page 295)

Treatment-related disease or poor-risk cytogenetics or molecular abnormalities

Clinical trial (category 2B) or Matched sibling or alternative donor HSCT (category 2B) or 1 to 2 cycles of high-dose cytarabine-based consolidation followed by autologous HSCT if no allogeneic transplant option available

See Surveillance (page 295)

PP Begin alternate donor search (unrelated donor or cord blood) if no appropriate sibling donor is available and patient is a candidate for an allogeneic HSCT.

*FLT3-ITD mutations are also emerging as a poor-risk feature in the setting of otherwise normal karyotype, and these patients should be considered for clinical trials where available. Controversy exists regarding allogeneic transplant for patients with favorable cytogenetics, only mutations in the absence of other poor prognostic features.


**Although both options -- (1) multiple cycles of dose-intensive consolidation and (2) one cycle of dose-intensive consolidation followed by autologous HSCT -- can produce good survival for patients with favorable cytogenetics, there are significant differences in toxicity. Patient age, comorbid conditions, and issues such as fertility and salvage options should be considered when choosing consolidation.

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CLASSIFICATION

 Favorable cytogenetic/molecular markers without prior MDS/therapy-related AML

Therapy-related AML/prior MDS or unfavorable cytogenetic/molecular markers

AML ≥ 60 y

PS 0-2

PS > 2

PS 0-3 with significant comorbidities

TREATMENT INDUCTION

Clinical trial

or

Standard-dose cytarabine (100-200 mg/m² continuous infusion x 7 d) with idarubicin1yy,zz 12 mg/m² or daunorubicin 45-60 mg/m² x 3 d or mitoxantrone

See Post-remission Therapy (page 294)

or

Low-intensity therapy (subcutaneous cytarabine; or 5-azacytidine or decitabine [category 2B])aaa

or

Intermediate-intensity therapy (clofarabine [category 2B])bbb

Clinical trial

or

Low-intensity therapy (5-azacytidine or decitabine [category 2B])aaa

or

Intermediate-intensity therapy (clofarabine [category 2B])bbb

or

Standard-dose cytarabine (100-200 mg/m² continuous infusion x 7 d) with idarubicin1yy,zz 12 mg/m² or daunorubicin 45-60 mg/m² x 3 d or mitoxantrone

See Post-remission Therapy (page 294)

Clinical trial

or

Low-intensity therapy (5-azacytidine or decitabine [category 2B])aaa

or

Intermediate-intensity therapy (clofarabine [category 2B])bbb

Best supportive care (hydroxyurea, transfusion support)

Clinical trial

or

Low-intensity therapy (5-azacytidine or decitabine [category 2B], or subcutaneous cytarabine)aaa

or

Best supportive care (hydroxyurea, transfusion support)

Note:

1aa Low-intensity therapy (5-azacytidine or decitabine) or mitoxantrone with anthracycline (idarubicin or daunorubicin) or mitoxantrone.

1bb Intermediate-intensity therapy (clofarabine).

1ccb Standard-dose cytarabine (100-200 mg/m² continuous infusion x 7 d) with idarubicin (12 mg/m² or daunorubicin 45-60 mg/m² x 3 d or mitoxantrone.

2cc Patients older than 75 years with significant comorbidities usually do not benefit from conventional chemotheraphy treatment. However, the rare patient with good or normal karyotype and no significant comorbidities may benefit from conventional chemotheraphy treatment.

2dd Response may not be evident before 3-4 cycles of treatment with hypomethylating agents (5-azacytidine, decitabine). Similar delays in response are likely with novel agents in clinical trials but end points will be defined by the protocol.

2ee Clofarabine is renally cleared. The recommended treatment dose for patients aged 60-70 years with normal CrCl (≥ 60 ml/min) is 30 mg/m². Clofarabine is not recommended for older patients with impaired renal function.

2ff Patients with blast counts > 50,000/mcl are at risk for tumor lysis and organ dysfunction secondary to leukostasis. Measures to rapidly reduce the white count include apheresis or hydroxyurea. Prompt institution of definitive therapy is essential.

2gg Patients older than 75 years with significant comorbidities usually do not benefit from conventional chemotheraphy treatment.

2hh Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.

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See Supportive Care (page 297).

kk See Monitoring During Therapy (page 298).

pp Begin alternate donor search (unrelated donor or cord blood) if no appropriate sibling donor is available and patient is a candidate for an allogeneic HSCT.

**Abbreviations:**

AML = acute myeloid leukemia

CR = complete remission

HSCT = hematopoietic stem cell transplantation

Idarubicin treatment compared with high doses of daunorubicin up to 80 mg/m² yields higher complete response rates and more complete responses after one course. (Pautas C, Merabet F, Thomas X, et al. Randomized study of intensified anthracycline doses for induction and recombinant interleukin-2 for maintenance in patients with acute myeloid leukemia age 50 to 70 years: results of the ALFA-9801 study. J Clin Oncol 2010;28:808-814). The CR rates and 2-y overall survival in patients between 60 and 65 years of age treated with daunorubicin 90 mg/m² is also comparable to the outcome for idarubicin 12 mg/m²; the higher dose daunorubicin did not benefit patients older than 65 years (Lowenberg B, Ossenkoppele GJ, van Putten W, et al. High-dose daunorubicin in older patients with acute myeloid leukemia. N Engl J Med 2009;361:1235-1248).
AML POSTREMISSION THERAPY

Age ≥ 60 y

Induction failure

| Complete response
| Clinical trial
| Reduced-intensity HSCT
| Standard-dose cytarabine (100-200 mg/m²/d x 5-7 d x 1-2 cycles) ± anthracycline (idarubicin or daunorubicin)
| Consider cytarabine 1-1.5 g/m²/d x 4-6 doses x 1-2 cycles for patients with good performance status, normal renal function, good or normal karyotype with favorable molecular markers
| Continue low-intensity regimens (5-azacytidine, decitabine) every 4-6 wk until progression

Marrow to document remission status upon hematologic recovery (4-6 wk)

Clinical trial

or

Reduced-intensity HSCT

or

Standard-dose cytarabine (100-200 mg/m²/d x 5-7 d x 1-2 cycles) ± anthracycline (idarubicin or daunorubicin)

or

Consider cytarabine 1-1.5 g/m²/d x 4-6 doses x 1-2 cycles for patients with good performance status, normal renal function, good or normal karyotype with favorable molecular markers

or

Continue low-intensity regimens (5-azacytidine, decitabine) every 4-6 wk until progression

See Response Criteria for Acute Myeloid Leukemia (page 298).

See Salvage Chemotherapy Options (page 298).

Reinduction therapy may be appropriate in certain circumstances, such as patients with long first remission. If a second CR is achieved, then consolidation with allogeneic HSCT should be considered.

Transplant should only be considered in the context of a clinical trial or if a remission is achieved.

See Response Criteria for Acute Myeloid Leukemia (page 298).

See Salvage Chemotherapy Options (page 298).

Reinduction therapy may be appropriate in certain circumstances, such as patients with long first remission. If a second CR is achieved, then consolidation with allogeneic HSCT should be considered.

Transplant should only be considered in the context of a clinical trial or if a remission is achieved.

See Response Criteria for Acute Myeloid Leukemia (page 298).

Patients who are deemed as strong candidates for stem cell transplant and who have an available donor should undergo transplantation in first remission.

Acute Myeloid Leukemia Version 2:2011

SURVEILLANCE
(AFTER COMPLETION OF CONSOLIDATION)

- CBC, platelets every 1-3 mo for 2 y, then every 3-6 mo up to 5 y
- Bone marrow aspirate only if peripheral smear abnormal or cytopenias develop
- Alternative donor search (including cord blood) should be initiated at first relapse in appropriate patients concomitant with institution of other therapy if no sibling donor has been identified

Early (< 12 mo)

Late (> 12 mo)

Age < 60

Relapse

Clinical trial or
Salvage chemotherapy followed by matched sibling or alternative donor HSCT

Clinical trial (strongly preferred)
or
Salvage chemotherapy followed by matched sibling or alternative donor HSCT or
Repeat initial successful induction regimen

Clinical trial (strongly preferred)
or
Best supportive care or
Salvage chemotherapy followed by matched sibling or alternative donor HSCT

Clinical trial (strongly preferred)
or
Treatment with initial successful regimen or Salvage chemotherapy followed by matched sibling or alternative donor HSCT or
Best supportive care

Age ≥ 60

Late (> 12 mo)

Salvage chemotherapy followed by matched sibling or alternative donor HSCT

Salvage chemotherapy followed by matched sibling or alternative donor HSCT

Salvage chemotherapy followed by matched sibling or alternative donor HSCT

Salvage chemotherapy followed by matched sibling or alternative donor HSCT

---

See Response Criteria for Acute Myeloid Leukemia (page 298).

See Salvage Chemotherapy Options (page 298).

Reinduction therapy may be appropriate in certain circumstances, such as patients with long first remission. If a second CR is achieved, then consolidation with allogeneic HSCT should be considered.

Transplant should only be considered in the context of a clinical trial or if a remission is achieved.
RISK STATUS BASED ON CYTOGENETICS AND MOLECULAR ABNORMALITIES

<table>
<thead>
<tr>
<th>RISK STATUS</th>
<th>CYTOGENETICS</th>
<th>MOLECULAR ABNORMALITIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Better-risk</td>
<td>inv(16)(^1) or t(16;16)(^1)</td>
<td>Normal cytogenetics:</td>
</tr>
<tr>
<td></td>
<td>t(8;21)(^1)</td>
<td>with NPM1 mutation or isolated CEBP A(^3) mutation in the absence of FLT3-ITD</td>
</tr>
<tr>
<td>Intermediate-risk</td>
<td>Normal cytogenetics +8</td>
<td>t(8;21), inv(16), t(16;16)</td>
</tr>
<tr>
<td></td>
<td>t(9;11)</td>
<td>with c-KIT 4 mutation</td>
</tr>
<tr>
<td></td>
<td>Other nondefined</td>
<td></td>
</tr>
<tr>
<td>Poor-risk</td>
<td>Complex (≥3 clonal chromosomal abnormalities)</td>
<td>Normal cytogenetics:</td>
</tr>
<tr>
<td></td>
<td>-5, 5q-, -7, 7q-</td>
<td>with FLT3-ITD mutation(^5)</td>
</tr>
<tr>
<td></td>
<td>-11q23 - non t(9;11)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>inv(3), t(3;3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>t(6;9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>t(9;22)(^2)</td>
<td></td>
</tr>
</tbody>
</table>

1 Other cytogenetic abnormalities in addition to these findings do not alter better risk status.
2 Philadelphia+ AML t(9;22) consider managing as myeloid blast crisis in CML. See NCCN Clinical Practice Guidelines in Oncology for Chronic Myelogenous Leukemia (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).
3 For CEBP A, the double mutation appears to confirm the relatively favorable prognosis.
4 Emerging data indicate that the presence of c-KIT mutations in patients with t(9;21) and, to a lesser extent, inv(16) confers a higher risk of relapse. These patients should be considered for clinical trials, if available.
5 FLT3-ITD mutations are considered to confer a significantly poorer outcome in patients with normal karyotype, and these patients should be considered for clinical trials where available. Controversy exists as to whether FLT3-TKD mutations carry an equally poor prognosis.

EVALUATION AND TREATMENT OF CNS LEUKEMIA\(^1\)

At diagnosis, neurologic symptoms\(^2\)

<table>
<thead>
<tr>
<th>CT/MRI to rule out bleed or mass effect</th>
<th>Negative mass effect</th>
<th>Lumbar puncture</th>
<th>Negative</th>
<th>Intrathecal chemotherapy(^3) 2x/wk until clear, then weekly x 4-6 wk(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive mass effect or increased intracranial pressure</td>
<td>Consider needle aspiration or biopsy</td>
<td>Consider needle aspiration or biopsy</td>
<td>Strongly consider RT(^3)-I followed by intrathecal chemotherapy 2x/wk until clear, then weekly x 4-6 wk(^1)</td>
<td></td>
</tr>
</tbody>
</table>

First CR screening, no neurologic symptoms\(^5\)

<table>
<thead>
<tr>
<th>Lumbar puncture</th>
<th>Negative</th>
<th>Positive</th>
<th>Intrathecal chemotherapy 2x/wk until clear(^1) or</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>If patient to receive high-dose cytarabine, follow-up with LP post completion of therapy to document clearance</td>
</tr>
</tbody>
</table>

1 Further CNS surveillance per institutional practice.
2 For patients with major neurologic signs or symptoms at diagnosis, appropriate imaging studies should be performed to detect meningeal disease, choromias, or CNS bleeding. LP should be performed if no mass, lesion, or hemorrhage detected on imaging study.
3 Induction chemotherapy should be started concurrently. However, for patients receiving high-dose cytarabine, because this agent crosses the blood-brain barrier, intrathecal therapy can be deferred until induction is completed.
4 Concurrent use of CNS RT with high-dose cytarabine, intrathecal methotrexate, or intrathecal liposomal cytarabine may increase risk of neurotoxicity.
5 Screening LP should be considered at first remission for patients with M4 or M5 morphology, or biphenotypic leukemia, or WBC > 100,000/mcL at diagnosis.
**Acute Myeloid Leukemia Version 2:2011**

**SUPPORTIVE CARE**

Variations exist among institutions, but the following issues are important to consider in the management of patients with AML.

**General**

- Blood products:
  - Leukocyte-depleted products used for transfusion
  - Irradiated blood products for patients receiving immunosuppressive therapy (fludarabine, HSCT).
  - Transfusion thresholds: RBCs for Hgb < 8 g/dL or per institutional guidelines or symptoms of anemia; platelets for patients with platelets < 10,000/mcL or with any signs of bleeding.
  - CMV screening for potential HSCT candidates may be considered.
  - Tumor lysis prophylaxis: hydration with diuresis, urine alkalization (may be contraindicated with increased phosphate), allopurinol administration, or rasburicase treatment. Rasburicase should be considered as initial treatment in patients with rapidly increasing blast counts, high uric acid, or evidence of impaired renal function.
  - Patients receiving high-dose cytarabine therapy (particularly those with impaired renal function) are at risk for cerebellar toxicity. Neurologic assessments, including tests for nystagmus, slurred speech, and dysmetria should be performed before each dose of cytarabine.
  - In patients exhibiting rapidly rising creatinine because of tumor lysis, high-dose cytarabine should be discontinued until creatinine normalizes.
  - Saline or steroid eye drops to both eyes 4 times daily for all patients undergoing high-dose cytarabine therapy until 24 h post completion of cytarabine.
  - Growth factors may be considered in older patients after chemotherapy is complete. Note that this use may confound interpretation of the bone marrow. Patient should be off GM-CSF or G-CSF for a minimum of 7 days before obtaining bone marrow to document remission.
  - Decisions regarding use and choice of antibiotics should be made by the individual institutions based on the prevailing organisms and their drug resistance patterns. Posaconazole has been shown to significantly decrease fungal infections when compared with fluconazole. Outcomes with other azoles, such as voriconazole, echinocandins, or amphotericin B, may produce equivalent results. Azoles should not be given during anthracyline chemotherapy, because azoles impair drug metabolism and can increase toxicity.

**APL**

- Clinical coagulopathy and overt bleeding:
  - Management of clinical coagulopathy and overt bleeding: aggressive platelet transfusion support to maintain platelets > 50,000/mcL, fibrinogen replacement with cryoprecipitate and fresh frozen plasma to maintain a level over 150 mg/dL, and maintain prothrombin time (PT) and partial thromboplastin time (PTT) close to normal values. Monitor daily until coagulopathy resolves.
  - Central venous catheter should not be placed until bleeding controlled.
  - Leukapheresis is not recommended in the routine management of patients with a high WBC count in APL because of the difference in leukemia biology; however, in life-threatening cases with leukostasis that is not responsive to other modalities, leukapheresis can be considered with caution.
  - APL differentiation syndrome:
    - Maintain a high index of suspicion of APL differentiation syndrome (fever, often associated with increasing WBC > 10,000/mcL usually at initial diagnosis or relapse, shortness of breath, hypoxemia, pleural or pericardial effusions). Close monitoring of volume overload and pulmonary status is indicated. Initiate dexamethasone at first signs or symptoms of respiratory compromise (hypoxia, pulmonary infiltrates, pericardial or pleural effusions) (10 mg BID for 3-5 d with a taper over 2 wks). Consider interrupting ATRA therapy until hypoxia resolves.
  - Arsenic trioxide monitoring:
    - Before initiating therapy
      - ECG for prolonged QTc interval assessment
      - Serum electrolytes (Ca, K, Mg) and creatinine
    - During therapy
      - Maintain K concentrations above 4 mEq/dL
      - Maintain Mg concentrations above 1.8 mg/dL
      - Reassess patients with absolute QTc interval > 500 ms (weekly during induction therapy and before each course of postremission therapy)
    - Myeloid growth factors should not be used.
    - Patients with relapsed APL or with hyperleukocytosis after ATRA may be at increased risk of CNS disease. Prophylactic intrathecal therapy is being evaluated in this group.

1. Patients who are allo-immunized should receive cross match compatible and/or HLA-specific blood products.
RESPONSE CRITERIA FOR ACUTE MYELOID LEUKEMIA

- Morphologic leukemia-free state
  - Bone marrow < 5% blasts in an aspirate with spicules
  - No blasts with Auer rods or persistence of extramedullary disease
  - If there is a question of residual leukemia, a bone marrow aspirate/biopsy should be repeated in 1 week.
- A bone marrow biopsy should be performed if spicules are absent from the aspirate sample.
- Complete remission
  - Morphologic CR - patient independent of transfusions
    - Absolute neutrophil count > 1000/mcL
    - Platelets ≥ 100,000/mcL
    - No residual evidence of extramedullary disease
  - Cytogenetic CR - cytogenetics normal (in those with previously abnormal cytogenetics)
  - Molecular CR - molecular studies negative
- Partial remission
  - Decrease of at least 50% in the percentage of blasts to 5% to 25% in the bone marrow aspirate and the normalization of blood counts.
- Patients not experiencing a complete response are considered treatment failures.
- Relapse after complete response is defined as reappearance of leukemic blasts in the peripheral blood or the finding of more than 5% blasts in the bone marrow, not attributable to another cause (e.g., bone marrow regeneration after consolidation therapy) or extramedullary relapse.

If there is a question of residual leukemia, a bone marrow aspirate/biopsy should be repeated in 1 week.

Induction:
- CBC, platelets daily (differential daily during chemotherapy and every other day after recovery of WBC > 500/mcL until either normal differential or persistent leukemia is documented), platelets every day while in hospital until platelet-transfusion independent.
- Chemistry profile, including electrolytes, BUN, creatinine, uric acid, and PO4, at least daily during active treatment until risk of tumor lysis is past. If patient is receiving nephrotoxic agents, closer monitoring is required through the period of hospitalization.
- Bone marrow aspirate/biopsy 7-10 days after completion of cytarabine-based chemotherapy to document hypoplasia. If hypoplasia is not documented or indeterminate, repeat biopsy in 7-14 days to clarify persistence of leukemia. If hypoplasia, then repeat biopsy at time of hematologic recovery to document remission. If cytogenetics were initially abnormal, include cytogenetics as part of the remission documentation.
- Postremission therapy:
  - CBC, platelets 2x/wk during chemotherapy
  - Chemistry profile, electrolytes daily during chemotherapy
  - Outpatient monitoring post chemotherapy: CBC, platelets, differential and electrolytes 2-3x/wk until recovery
  - Bone marrow only if peripheral blood counts abnormal or failure to recover counts within 5 wk
- Patients with high-risk features, including poor-prognosis cytogenetics, therapy-related AML, prior MDS, or patients who require 2 or more inductions to experience a CR, are at increased risk for relapse and may be considered for early unrelated donor search, as indicated on page 288.

SALVAGE CHEMOTHERAPY REGIMEN OPTIONS
- Cladribine + cytarabine + GCSF ± mitoxantrone or idarubicin
- High-dose cytarabine + anthracycline (if not received previously in treatment)
- Fludarabine + cytarabine + GCSF ± idarubicin
- Mitoxantrone + etoposide + cytarabine (MEC)

2 This is clinically relevant only in APL and Ph+ leukemia at the present time.
3 PR’s are only useful in assessing potential activity of new investigational agents, usually in phase I trials, and should not be considered a therapy goal for standard therapy.

MONITORING DURING THERAPY
incorporates flow cytometry to define an immunophenotype, which separates myeloid from lymphoid blasts. AML is then subcategorized into 8 entities based on degree of differentiation. The FAB classification (1976) sets the threshold between high-grade myelodysplastic syndromes (MDS) and AML at 30% blasts.

The 1999 WHO classification was designed to include newer prognostic factors, such as chromosome translocations, and evidence of dysplasia, either through morphology or history, to attempt to predict biologic responsiveness and thereby allow physicians to identify subgroups of patients who might benefit from specific treatment strategies. This classification created a minimum of 17 subclasses of AML. Based on epidemiologic data indicating that patients with MDS with 20% to 30% blasts had equally as poor survival as those with AML with greater than 30% blasts, the WHO lowered the threshold for diagnosing AML to greater than 20% blasts and abolished the MDS category of refractory anemia with excess blasts in transformation (RAEB-T). In addition, WHO allows AML to be diagnosed regardless of the percentage of marrow blasts in patients with abnormal hematopoiesis and characteristic clonal structural cytogenetic abnormalities, including t(15;17), t(8;21), and inv(16) or t(16;16).

In 2003, the International Working Group (IWG) for the diagnosis and standardization of response criteria accepted the cytochemical and immunophenotypic criteria of WHO as the standard for diagnosing AML, including the reporting of dysplasia according to morphology. However, no evidence shows that dysplasia represents an independent risk factor, because it is frequently linked to poor-risk cytogenetics.

Based on the recommendations of the IWG, some cooperative group and most institutional phase II and pharmaceutical trials adopted the WHO threshold for percentage marrow blasts as the criterion for diagnosing AML, and their definitions of complete remission and other categories of response. Some large cooperative group trials have retained the FAB criteria to compare study populations in large phase III trials in which the control arm of a current trial is based on the outcome of a prior trial that used FAB definitions.

The WHO revised the diagnostic and response criteria for AML in 2008 to include additional recurrent genetic abnormalities created by reciprocal translocations, and a new provisional category for some of the molecular markers that have prognostic impact.

Although roughly 75% of patients with acute leukemia can be categorized as myeloid or lymphoid lineage based on routine cytochemistry, immunophenotyping is necessary for proper diagnosis in a subset of patients, particularly those with undifferentiated or minimally differentiated morphology that may be negative for cytochemical myeloperoxidase or combined esterases. A diagnosis of acute lymphoblastic leukemia (ALL) requires the presence of at least 2 lymphoid markers; most are also terminal deoxynucleotidyl transferase (TdT)–positive. The guidelines suggest that either of these complementary techniques can be used at the discretion of the pathology departments of the individual institutions. Some cases may still show evidence of both myeloid and lymphoid antigen expression on the leukemic cells. These cases require consultation with an experienced hematopathologist. Aberrant expression of differentiation antigens present at diagnosis may allow tracking of residual abnormal cells using flow cytometry in follow-up samples that may look normal using conventional morphology techniques. However, the role of immunophenotyping and molecular markers in monitoring minimal residual disease in adult AML remains an area of research interest.

Although cytogenetic information is usually unknown when treatment is initiated in patients with de novo AML, karyotype represents the single most important prognostic factor for predicting remission rate, relapse, and overall survival. In a retrospective review of 1213 patients with AML treated on CALGB protocols, the 5-year survival rates for those with favorable-, intermediate-, and poor-risk cytogenetics were 55%, 24%, and 5%, respectively. Therefore, it is critical to obtain adequate samples on marrow or peripheral blood at diagnosis to do full karyotyping and fluorescence in situ hybridization (FISH) probes for the most common abnormalities. In addition to basic cytogenetic analysis, new molecular markers are helping to refine prognostics groups particularly in patients with a normal karyotype. These include FMS-like tyrosine kinase 3 (FLT3), c-KIT, nucleophosmin member 1 (NPM1), and CEBPA (CCAAT/enhancer binding protein alpha) mutations. Tests for these molecular markers are not commonly available in the community; it is important to preserve additional aliquots of
Acute Myeloid Leukemia

cryopreserved marrow from diagnosis for molecular diagnostic tests in patients with normal karyotype.

The 2 most frequent molecular mutations with prognostic impact are mutations of the FLT3 gene encoding a transmembrane growth factor receptor and mutations of the NPM1 gene, which encodes a shuttling protein within the nucleolus. Both mutations may be found in 40% to 50% of patients with normal cytogenetics either as isolated or double mutations. A single NPM1 mutation that localizes to the cytoplasm confers a higher complete remission rate, and improved event-free and overall survivals for patients with normal karyotype, similar to those with favorable cytogenetics. Two major classes of activating FLT3 mutations have been identified in patients with AML: internal-tandem duplications (ITD) and tyrosine kinase domain (TKD) point mutations. Several large studies have shown that patients with isolated FLT3-ITD mutations have a poor prognosis, with a disease-free survival rate of 20% to 25% at 2 years, particularly if both alleles are mutated. Patients who have both NPM1 and FLT3-ITD mutations have an outcome intermediate between those groups.

Internal tandem duplications of the mixed lineage leukemia (MLL) gene have also been associated with a poor prognosis. In patients with favorable karyotypes, t(8;21) or inv(16), the presence of a mutation in c-KIT significantly increases the risk of relapse. Although none of these abnormalities affect the initial treatment, they provide information that may influence subsequent treatment decisions. Research into basic leukemia biology using banked samples from clinical trials may provide keys to altered cellular pathways, which may lead to new treatment options. The algorithm summarizes the new risk stratification that incorporates the molecular data along with cytogenetics.

Extramedullary presentation, including central nervous system (CNS) disease, is an uncommon event in AML. Patients with significant signs or symptoms of CNS disease at presentation should be evaluated with appropriate imaging techniques, such as radiography, CT, or MRI, for intracranial bleeding, leptomeningeal disease, or mass lesions in either the brain or spinal cord.

If symptoms persist and bleeding and mass lesions are excluded, a lumbar puncture should be performed for diagnostic and possible therapeutic purposes once coagulopathy has been corrected and adequate platelet support is available. Routine screening lumbar punctures are not warranted in AML at diagnosis. However, for patients at high risk for CNS disease, such as those with monocytic differentiation (M4 or M5) or high WBC counts (> 100,000/mcL) at presentation, a diagnostic lumbar puncture should be included as part of the documentation of remission status.

Coagulopathy is fairly common at presentation in many leukemias; it is good clinical practice to screen for this problem with prothrombin time, partial thromboplastin time, and fibrinogen as part of the initial workup and before any invasive procedure. The need for a cardiac evaluation should be determined by individual risk factors, such as patient and family history or previous malignancy treated with cardiotoxic drugs or thoracic radiation. Human leukocyte antigen (HLA) typing should be performed in all patients with newly diagnosed AML for whom allogeneic hematopoietic stem cell transplantation (HSCT) would be considered. HLA typing of family members is recommended for patients younger than 55 years who do not have favorable-risk cytogenetics. Tissue typing should be broadened to include unrelated donor searches in patients younger than 55 years with karyotypes or molecular abnormalities deemed high-risk or antecedent MDS/therapy-related AML. For patients in the high-risk group, a donor search should begin during recovery from induction chemotherapy rather than waiting for remission. Many institutions also use HLA typing to select platelet donors for allogeneic transplantation.

For patients who present with solitary extramedullary disease (often referred to as granulocytic sarcoma or chloroma) without overt marrow disease, initial treatment should still be based on systemic induction chemotherapy. Radiation or surgical resection may be incorporated with systemic chemotherapy in emergent situations, but if these modalities are necessary, they should optimally be deferred until count recovery to avoid excess toxicity.

**Principles of Treatment**

Treatment of acute leukemia has been divided into induction chemotherapy and postremission (or consolidation) therapy. Although the first step in controlling the disease is to achieve remission, the patient must also emerge from the induction phase able to tolerate...
subsequent more-intensive treatments during consolidation to experience durable disease control. Patients who do not undergo postremission therapy will experience relapse, usually within 6 to 9 months.

The induction strategy is influenced by individual patient characteristics, such as age, presence of comorbid conditions affecting performance status, and preexisting myelodysplasia. This is particularly true of older patients with AML. Patients whose performance status would make them poor candidates for the standard antineoplastic regimens may still be able to participate in clinical trials using epigenetic agents designed to target this underserved patient population. If a clinical trial is not an option, then low-intensity therapy or supportive care may be appropriate. In younger patients, strategies for consolidation are based on the potential risk of relapse, with higher-risk patients undergoing more aggressive therapy. Cytogenetic and molecular mutations are the most significant prognostic indicators, with failure to achieve remission after 1 cycle of induction therapy and tumor burden (WBC ≥ 100,000/mcL) included as poor risk factors for long-term remission. Response is assessed at several points during treatment, based on bone marrow morphology and cytogenetic and molecular responses. Definitions of complete and partial response and disease relapse are provided on page 298.

Finally, all patients require attentive supportive care for the underlying leukemia (i.e., tumor lysis syndrome) and the side effects of chemotherapy. These measures are summarized on page 297.

**APL**

APL has a distinctive morphology and clinical presentation with coagulopathy that sets it apart from the other FAB morphologic subgroups. The translocation of the promyelocytic leukemia (PML) gene on chromosome 15 adjacent to the retinoic acid receptor (RAR) alpha gene on chromosome 17 produces a fusion protein that can be quantitatively monitored using polymerase chain reaction (PCR) to document disease burden and ultimately confirm “molecular remission.” The unique ability of all-trans retinoic acid (ATRA) to produce differentiation in APL blasts can reverse the coagulopathy, which is the major cause of death during induction. To minimize early induction mortality from coagulopathy, patients presumed to have APL based on morphology, immunophenotype, and/or coagulopathy with positive disseminated intravascular coagulation screen should start ATRA and anthracycline promptly without waiting for molecular confirmation. If the initial clinical diagnosis of APL is not confirmed with FISH or PCR, ATRA should be discontinued and standard AML induction continued.

**Induction Therapy**

The evolution of treatment strategies for APL based on clinical observation and well-constructed clinical trials is one of the most rewarding sagas of modern hematology. In 1988, a group in Shanghai reported that ATRA given as single agent induced complete remission rates of 85%. The first North American Intergroup study confirmed a 70% complete remission rate with single-agent ATRA, which was equivalent to rates seen with conventional doses of cytarabine (Ara-C) and daunorubicin.

The French APL 93 trial compared ATRA plus chemotherapy (Ara-C and daunorubicin) and ATRA followed by chemotherapy. Complete remission rates were 92% in both arms, but the relapse rate at 2 years was 6% in the combined group versus 16% for the sequential group.

Induction regimens were pared down to ATRA and idarubicin in the Italian GIMEMA 93 and Spanish PETHEMA LPA 94 trials, which produced complete remission rates of 95%, raising the question of whether Ara-C was needed in APL induction. Patients with elevated WBC counts were commonly observed to have high-risk disease, based on higher deaths during induction and increased rates of relapse.

As an outgrowth of the PETHEMA LPA 94 trials, Sanz et al. developed a risk stratification based solely on WBC and platelet counts at presentation. The induction regimen remained the same (idarubicin and ATRA), but ATRA was added to consolidation cycles 1 through 3 for all but low-risk patients (WBC ≤ 10,000/mcL and platelets > 40,000/mcL). The complete remission rate in this trial was 91%, with almost all failures attributed to hemorrhage, infection, or differentiation syndrome. Factors predictive of death during induction were WBC count greater than 10,000/mcL, age older than 60 years, creatinine level of 1.4 or greater, and male sex.

In 2006, Ades et al. reported the outcome of the French APL 2000 trial, in which 340 patients younger than 60 years with a WBC count less than...
10,000/mcL were randomized to receive ATRA (45 mg/m²) and daunorubicin (60 mg/m²/d for 3 days) as induction therapy with or without Ara-C (200 mg/m²/d for 7 days). Those randomized to Ara-C in induction also received Ara-C in consolidation. Patients with WBC counts greater than 10,000/mcL or age older than 60 years all received Ara-C. Although the complete remission rates were similar in the randomized groups (99% with and 94% without Ara-C), those receiving Ara-C had a lower 2-year cumulative incidence of relapse that translated into an improved event-free survival rate (93% vs. 79%, respectively, at 2 years). In patients with WBC counts greater than 10,000/mcL, the complete remission rate was 97% and the 2-year disease-free survival rates were 89% for those younger than 60 years and 79% for those older than 60 years. A report of a joint analysis of the outcomes in the PETHEMA 99 and French APL 2000 trials in patients younger than 65 years showed that in patients with WBC counts less than 10,000/mcL, complete remission rates were similar, but the relapse rates at 3 years were lower (4.2%) in the PETHEMA trial, which used ATRA during consolidation, than in the APL 2000 Ara-C-containing regimen (14.3%; P = .03). However, for patients with WBC counts greater than 10,000/mcL, the Ara-C-containing protocol had better rates of complete remission (95% vs. 84%) and 3-year survival (92% vs. 81%; P = .18). The second North American Intergroup Trial (NAIT) also used ATRA (45 mg/m²), daunorubicin (50 mg/m²/d for 4 days), and Ara-C (200 mg/m²/d for 7 days), and showed similar initial complete remission rates. Consolidation in this trial differed in that 2 cycles of a novel agent, arsenic trioxide, were given after induction and before the final 2 cycles of anthracycline.

All 3 regimens offer excellent outcomes, with the choices influenced by risk group, age, and cardiovascular risks. The panel recommends that patients with APL be treated with one of the regimens established from the clinical trials and that the regimen be used consistently through all components, rather than mixing induction from one trial with consolidation from a second trial. The NCCN Guidelines are broken down by ability to tolerate anthracyclines and the PETHEMA risk classification based on WBC count at diagnosis. Patients with APL who can tolerate anthracyclines are stratified into risk groups based on WBC counts. In general, the panel has preferentially listed regimens of equivalent efficacy for a given risk group based on ease of administration. For low- or intermediate-risk patients (WBC < 10,000/mcL), the panel recommends initial induction with ATRA plus idarubicin alone (category 1); ATRA plus daunorubicin and Ara-C (category 1 for those on French APL 2000 protocol); or enrollment in a clinical trial. For high-risk patients (WBC > 10,000/mcL), the panel prefers regimens that include Ara-C along with ATRA plus daunorubicin over ATRA plus idarubicin because of higher disease-free survival rates at 2 years, although the complete remission rates reported in the trials were very comparable.

Arsenic trioxide (ATO) has also been found to be a potent promoter of apoptosis in APL cells. In 2004, Shen et al. published outcomes on single-agent ATRA, single-agent ATO, or the combination of both. Although complete remission rates exceed 90% in all 3 arms, the decline in quantity of PML/RAR alpha fusion protein as measured by quantitative PCR was significantly higher with the combination. Hematologic recovery was quicker and relapse-free survival was improved at 18 months.

Subsequently, Estey et al. treated 25 patients with low- and intermediate-risk APL using a similar combination of ATRA and ATO, and 19 high-risk patients were treated using ATRA and ATO combined with gemtuzumab ozogamicin, 9 mg/m², on day 1 of induction therapy. Complete remission occurred in 24 patients with low-risk disease and 15 patients with high-risk disease. The authors suggested that ATRA plus ATO may be an alternative to chemotherapy in patients with low- and intermediate-risk untreated APL and, when combined with gemtuzumab ozogamicin, may improve outcomes in high-risk patients. However, in October 2010, the FDA withdrew the prior approval of gemtuzumab ozogamicin for the treatment of older patients with relapsed AML because of a lack of clinical benefit, and therefore this drug is no longer commercially available in the United States. These NCCN Guidelines indicate that ATRA plus ATO is an alternative for patients who cannot tolerate anthracycline therapy.

Consolidation Therapy

Because the differentiating action of ATRA occurs over a longer period than the cyto reduction of conventional chemotherapy, early marrow evaluations for hematologic response at day 7 to 14 after induction are misleading and may lead to overtreatment.
Marrow evaluation is not recommended until recovery of blood counts, which usually occurs 4 to 6 weeks after therapy. Cytogenetics is usually normal by this point, but molecular remission often requires at least 2 cycles of consolidation. All consolidation regimens have high cumulative doses of cardiotoxic agents. Therefore, cardiac function of the patient should be assessed before initiating each anthracycline- or mitoxantrone-containing consolidation cycle.

The goal of consolidation therapy for APL is the conversion of a morphologic and cytogenetic remission into a durable molecular remission. Data from the 2 sequential PETHEMA trials, which produced the current risk model, were used to construct subsequent trials that intensify therapy for the high-risk groups. In the second PETHEMA trial (LPA 99), 15 days of ATRA (45 mg/m²) were added to each of 3 cycles of anthracycline consolidation. In the low-risk group, no difference was seen in rates of relapse (3%–6%) or 3-year disease-free survival (93%–97%) with the use of ATRA compared with a similar consolidation without ATRA in trial LPA 94. For the intermediate-risk group, the relapse rate was 2.5% versus 14% in the historic control, with a 3-year disease-free survival of 97% versus 82%. Although the addition of ATRA to the high-risk group improved rates of relapse and disease-free survival, the rates of 21% and 77%, respectively, indicate that there is room for improvement. The new AIDA-2000 trial of the Italian GIMEMA group has confirmed that inclusion of ATRA in consolidation significantly improves outcome.

In the French APL 2000 trial, which randomized Ara-C with daunorubicin consolidation without ATRA, the low- and intermediate-risk groups had a 2-year disease-free survival rate of 93% with Ara-C versus 77% for the group without. Thus the outcomes for consolidation with anthracycline plus ATRA or anthracycline plus Ara-C are comparable for patients with intermediate-risk APL. For all high-risk patients younger than 60 years, the addition of Ara-C seems to offer some benefit, with a 2-year disease-free survival rate of 89%.

In the new nonrandomized Spanish trial (LPA 2005), Ara-C (1 g/m²/d for 4 days) was added to the combination of ATRA (45 mg/m²/d for 15 days) and idarubicin (7 mg/m²/d for 4 days) for consolidation in high-risk patients younger than 60 years. The high-risk patients treated with Ara-C had a significantly lower relapse rate at 3 years (11%) than those treated without Ara-C (21%). The LPA 2005 trial also began to investigate reducing toxicity during consolidation therapy in low- and intermediate-risk patients through a dose reduction of mitoxantrone (from 10 mg/m²/d for 5 days to 10 mg/m²/d for 3 days) and a small dose reduction of idarubicin (from 7 mg/m²/d for 4 days to 5 mg/m²/d for 4 days). Results showed that lowering the dose of mitoxantrone reduced toxicity and decreased length of hospital stay while maintaining antileukemic activity.

NAIT also investigated decreasing toxicity during consolidation through incorporating ATO into the consolidation schema directly after remission occurred. This trial randomized patients to receive either 2 courses of 25 days of ATO (5 days per week for 5 weeks) immediately after experiencing complete remission followed by a standard postremission regimen with 2 more courses of ATRA plus daunorubicin, or only 2 courses of ATRA plus chemotherapy. Those who were treated with ATO, particularly those with high-risk disease, showed significantly better event-free and overall survival rates. The overall outcomes do not seem to be superior to the less-complex consolidation schedules in either of the 2 most recent European trials for patients in the low- and intermediate-risk groups, but inclusion of ATO appeared to offer improved survival for high-risk disease. The consolidation period in the NAIT protocol is longer and maybe difficult for some patients. The potential benefits of ATO use in consolidation may be that it confers a lesser risk of long-term cardiovascular complications and perhaps a lower risk of secondary myelodysplasia.

For patients with high-risk disease, the panel suggests including Ara-C as used in the French APL 2000 trial and PETHEMA LPA 2005, or 2 cycles of ATO followed by 2 additional cycles of standard chemotherapy as used in the U.S. Intergroup trial for consolidation. When using an Ara-C containing regimen, dose adjustments of Ara-C may be needed for older patients or those with renal dysfunction. For low-risk patients, the panel has positioned the revised PETHEMA LPA 2005 regimen slightly higher than either the French APL 2000 or the NAIT because of ease of administration and decreasing toxicity. However, all 3 regimens yield excellent results. For the intermediate-risk group, outcomes are very similar as long as one regimen is followed consistently from induction through consolidation.

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In patients who received ATRA and ATO for induction therapy but could not tolerate anthracyclines, the reported trials continued with repeated cycles of ATRA and ATO after induction. Based on these reports, the panel recommends consolidation therapy with ATO (0.15 mg/kg intravenous daily for 5 days per week every other month for 4 cycles) and ATRA (45 mg/m² in divided doses daily orally during 1 week monthly for 7 cycles).

**Postconsolidation or Maintenance Therapy**

After consolidation therapy, patients are assessed for molecular remission using RT-PCR techniques on bone marrow samples. For those who are PCR-negative, a 1- to 2-year course of ATRA maintenance therapy has been recommended, which may be combined with 6-mercaptopurine (6MP) and methotrexate.

The recommendations for maintenance ATRA arose from several early trials that showed superior relapse-free survival for patients receiving ATRA alone or in combination as maintenance. The French APL 93 trial showed decreased relapse rates at 2 years for ATRA (21%), 6MP, and methotrexate (13%), and ATRA plus 6MP and methotrexate (8%), versus no maintenance (35%). Results of a longer follow-up of the APL 93 trial show a beneficial effect of maintenance treatment with intermittent ATRA and continuous 6MP and methotrexate, with an additive effect of the 2 modalities. The study data showed that maintenance treatment reduced the incidence of early relapses without increasing the incidence late relapses. Patients with a WBC count higher than 5000/µL benefitted most from maintenance therapy. The relapse rate dropped from 68.4% with no maintenance to 20.6% with combined ATRA plus chemotherapy maintenance. In patients with WBC counts lower than 5000/µL, the 10-year relapse rate decreased from 29.2% without maintenance to 11.5% with combined maintenance.

The first U.S. Intergroup trial showed superior disease-free survival among patients receiving maintenance ATRA compared with no maintenance. However, data from the All-Trans Retinoic Acid and Idarubicin (AIDA) trial suggest that patients who are molecularly negative at end of consolidation experience no benefit from maintenance.

As consolidation regimens have evolved to incorporate ATRA or ATO into consolidation, the role of maintenance chemotherapy is less clear, particularly for patients with low-risk disease who achieve a molecular remission at the end of consolidation. An international cooperative group trial (SWOG 0521) examined the need for maintenance in low-/intermediate-risk patients. The studies showing benefit for maintenance were performed before ATRA was used for consolidation. The conflicting data indicate that benefit of maintenance depends on prior induction and consolidation therapy. Therefore, it would be appropriate to use maintenance in conjunction with protocols in which it has been shown to confer benefit.

At completion of consolidation, RT-PCR should be performed on a marrow sample to document molecular remission. Subsequent monitoring of patients with PCR can be performed using peripheral blood, although the technique is more sensitive and may show earlier signs of relapse when performed on a marrow sample. Monitoring is recommended at a minimum of every 3 months for 2 years during maintenance to detect molecular relapse in patients with intermediate- and high-risk disease. Clinical experience indicates that risk of relapse is low in patients with low-risk disease experiencing molecular remission at completion of consolidation, and that monitoring may not be necessary outside the setting of a clinical trial. At the current level of resolution, a change from PCR-negative to -positive should be confirmed with bone marrow in a reliable laboratory within 4 weeks. If molecular relapse is confirmed by a second positive test, intervention should be strongly considered. If the second test was negative, maintenance therapy and frequent monitoring every 2 to 3 months for an additional 2 years is strongly suggested to assure that the patient remains negative. Testing should be performed in the same laboratory to maintain a consistent level of sensitivity. In patients who develop cytopenias and have a negative RT-PCR, a marrow analysis is recommended to evaluate for new cytogenetic abnormalities, because secondary MDS and AML have occurred after APL therapy.

**Management of Relapse**

ATO is the recommended therapy for patients who remain molecularly positive at completion of consolidation or subsequently show molecular relapse. As a single agent, it produced complete remission rates of 80% to 90% in patients with hematologic relapse, and molecular remissions in 70% to 80%
of those patients. ATRA and ATO seem to be synergistic, and this combination could be considered in patients who did not receive ATRA during consolidation.\textsuperscript{32–34} However, a small randomized study of 20 patients with relapsed APL all previously treated with ATRA-containing chemotherapy showed no improvement in response after ATRA was added to ATO compared with ATO alone.\textsuperscript{41}

A small percentage of relapsed APL has a CNS component.\textsuperscript{32,43} Therefore, for patients who are in second morphologic remission, the panel strongly recommends intrathecal therapy as CNS prophylaxis.

Patients who experience a molecular remission after second-line therapy should be considered for autologous HSCT if they have no contraindications to high-dose therapy. In a recent retrospective study by the European APL Group, patients who received a PCR-negative autograft had a 7-year overall survival rate of 75%, compared with 52% in those receiving an allogeneic HSCT.\textsuperscript{44} The differences in survival are accounted for by a higher treatment-related mortality in the allogeneic group, which influences the guideline recommendations to reserve allogeneic transplantation for those who have persistent disease despite salvage therapy. For patients in second complete remission who have contraindications to HSCT, continued therapy with ATO for 6 cycles is recommended in the absence of a clinical trial.

**Supportive Care**

Specific supportive care issues should be considered when treating patients with APL. Therapy for APL is often associated with a constellation of symptoms and physiologic abnormalities, including fluid retention, dyspnea, episodic hypotension, pulmonary infiltrates, and pulmonary or pericardial effusions now referred to as differentiation syndrome. Early in treatment involving either ATRA or arsenic as single agents or in combination, patients may begin to develop evidence of differentiation syndrome. These patients develop fever, fluid retention, and rapidly rising WBC counts to greater than 10,000/mcL. These patients should be closely monitored for hypoxia and the development of pulmonary infiltrates or pleural effusion. Differentiation syndrome and hemorrhage are the leading causes of death during induction. Early recognition and prompt initiation of steroids are the keys to dealing with this complication. In some studies, low mortality and morbidity rates were seen when corticosteroids were administered prophylactically in patients presenting with high WBC counts.\textsuperscript{37,45}

Kelaidi et al.\textsuperscript{46} assessed the outcomes of patients with high WBC counts (> 10,000/mcL) enrolled in the APL 93 and APL 2000 trials. The factor in supportive care that had an effect on early induction deaths was shown to be the use of dexamethasone, 10 mg every 12 hours, beginning on day 1 for patients on APL 2000. The early death rate from differentiation syndrome dropped from 8 of 139 in APL 93 to 2 of 133 in APL 2000. The panel recommends giving prophylactic steroids to patients with a WBC count greater than 10,000/mcL to prevent differentiation syndrome. The panel has provided management recommendations in the Supportive Care section of the algorithm. For patients with WBC counts greater than 10,000/mcL or symptoms of differentiation syndrome, the panel recommends treatment with dexamethasone, 10 mg, twice daily for 3 to 5 days, and then tapering the dose over 2 weeks. ATRA may need to be suspended during the initial acute symptomatic period but may be restarted when symptoms improve. Other factors that have been reported to increase the risk of differentiation syndrome are a high body mass index and age older than 40 years.

Leukapheresis is not recommended in the routine management of patients with APL with high WBC counts because of the difference in leukemia biology. However, in a life-threatening case with leukostasis that is not responsive to other modalities, leukapheresis can be considered with caution.

Because coagulopathy is common in patients with APL, it is good clinical practice to screen for this problem with prothrombin time (PT), partial thromboplastin time (PTT), and fibrinogen as part of the initial workup and before any invasive procedure. Clinical coagulopathy is managed with aggressive transfusion support to maintain platelets at 50,000/mcL or greater, fibrinogen replacement with cryoprecipitate and frozen plasma to maintain a level of 150 mg/dL, and maintaining levels of PT and PTT close to normal. Patients with clinical coagulopathy must be monitored daily until the condition resolves.

ATO therapy may prolong the QT interval, making patients susceptible to ventricular arrhythmias. Therefore, before each cycle of therapy, an electrocardiogram (ECG or EKG) is recommended to assess prolonged QT interval. Routine monitoring
weekly during therapy is also suggested for older patients. Serum electrolytes should also be monitored before and during therapy to maintain electrolytes (calcium ≥ 9.0, potassium ≥ 4.0, magnesium ≥ 1.8) in the upper normal range. Other drugs that prolong the QT interval should be avoided during ATO to minimize the risk of cardiac arrhythmias. Patients with an absolute QT interval greater than 500 m/s should be reassessed.

A 4% incidence of CNS relapse was seen in patients with a WBC count greater than 10,000/mcL in the French APL 93 trial. In APL 2000, the high-risk population received 5 doses of intrathecal chemotherapy using a combination of methotrexate, Ara-C, and steroids on count recovery after induction. They also received a higher dose of Ara-C (2 g/m²) during the second consolidation cycle compared with 1 g/m² in APL 93. No CNS relapses occurred in APL 2000 versus 5 cases in APL 93. Although the original trial used high-dose Ara-C as the second consolidation, some investigators suggest using it earlier, particularly in patients who are not receiving intrathecal therapy for prophylaxis.

**AML**

Most initial treatment decisions for AML are based on age, history of prior myelodysplasia or cytotoxic therapy, and performance status. Although karyotype is the most powerful predictor of disease-free survival, induction chemotherapy usually will be initiated before this information is available. The intent of traditional induction chemotherapy is to produce a major reduction in the leukemic burden and restore normal hematopoiesis.

Recommendations for induction chemotherapy for patients with AML consider 60 years of age as a therapeutic divergence point. This is based on the higher prevalence of unfavorable cytogenetics and antecedent myelodysplasia, along with a higher incidence of multidrug resistance in patients older than 60 years and an increased frequency of comorbid medical conditions that affect the ability to tolerate intensive treatment. Because complete remission rates rarely exceed 70% in younger patients and 50% in older patients, substantial opportunity exists for innovative clinical trials for both patient populations. These guidelines consider patients older and younger than 60 years old separately.

**Patients Younger Than 60 Years**

**Induction Therapy:** Standard induction regimens are appropriate for patients younger than 60 years who have no antecedent hematologic disease, such as MDS or treatment-related secondary AML. These regimens are based on a backbone of Ara-C and an anthracycline and have changed little in the past 25 years. Historically, in most large cooperative group trials, daunorubicin has been the most commonly used anthracycline at doses of 45 to 60 mg/m². However, idarubicin, which has a longer intracellular retention time, is used at doses of 12 mg/m² for 3 days and has had comparable remission rates, with fewer patients requiring additional therapy at day 15 to experience remission. Complete remission rates for patients aged 50 years or younger have consistently ranged from 60% to 70% in most large cooperative group trials of infusional Ara-C and anthracycline. A recent ECOG study reported a significant increase in complete remission rates (71% vs. 57%) and overall survival using daunorubicin, 90 mg/m², for 3 days versus 45 mg/m² for 3 days in patients younger than 60 years. The survival benefit was restricted to patients with favorable- and intermediate-risk cytogenetic profiles and those younger than 50 years.

A European trial comparing idarubicin, 12 mg/m², for either 3 or 4 days and daunorubicin, 80 mg/m², for 3 days in patients between ages 50 and 70, showed complete remission rates of 83% in patients treated with idarubicin, 12 mg/m², for 3 days versus 70% in those treated with daunorubicin (P = .024). No difference was seen in relapse rate, event-free survival, or overall survival among the arms. Infusional Ara-C for 7 days combined with either idarubicin or escalated daunorubicin is a category 1 recommendation.

For patients with impaired cardiac function, other regimens that combine a nonanthracycline (e.g., fludarabine or topotecan) with Ara-C have been published.

Two large cooperative clinical trials explored dose-intensive Ara-C therapy during induction. An Australian Leukemia Study Group trial randomized 301 patients younger than 60 years to receive either high-dose Ara-C (3 g/m² every 12 hours on days 1, 3, 5, and 7 for a total of 24 g/m²) or standard Ara-C therapy (100 mg/m²/d for 7 days through continuous infusion). Both arms received daunorubicin (50 mg/m² on days 1–3) and etoposide (75 mg/m²/d for 7 days). The complete remission rates were equiva-
lent in both arms (71% and 74%, respectively), although treatment-related morbidity and mortality were higher in the high-dose arm. Patients in both arms received only 2 cycles of standard-dose Ara-C, daunorubicin, and etoposide for consolidation. Median remission duration was 45 months for the dose-intensive arm compared with 12 months for the standard treatment arm.

A SWOG study\textsuperscript{55} randomized patients to receive either high-dose Ara-C (2 g/m\textsuperscript{2} every 12 hours for 6 days for a total of 24 g/m\textsuperscript{2}) or standard-dose Ara-C (200 mg/m\textsuperscript{2}/d for 7 days). Patients in both arms also received daunorubicin (45 mg/m\textsuperscript{2}/d for 3 days). Patients receiving high-dose Ara-C induction therapy received a second high-dose cycle for consolidation, and patients in the standard-dose treatment arm were randomized to receive either 2 cycles of standard-dose Ara-C consolidation or 1 cycle of high-dose Ara-C plus daunorubicin consolidation. The complete response rates were again equivalent: 55% for the high-dose Ara-C treatment arm compared with 58% for the standard-dose arm in patients younger than 50 years; and 45% for high-dose Ara-C versus 53% for standard-dose therapy for patients 50 to 65 years of age. Patients in the high-dose Ara-C arm experienced higher treatment-related mortality (12% vs. 5%) and neurologic toxicity.

Younger patients who received both high-dose Ara-C induction and consolidation in the SWOG trial had the best survival and disease-free survival rates (52% and 34%, respectively) at 4 years compared with those receiving standard induction and consolidation (34% and 24%, respectively) or standard induction with high-dose consolidation (23% and 14%, respectively). However, the percentage of patients experiencing a complete remission who did not proceed to consolidation was twice as high in the high-dose Ara-C induction arm. Risks for neurotoxicity and renal insufficiency are increased with high-dose Ara-C, and therefore renal and neurologic function should be closely monitored. In a CALGB trial,\textsuperscript{54} patients who received induction therapy with standard-dose Ara-C and daunorubicin or 3 to 4 courses of high-dose Ara-C consolidation also had a 44% probability of a 4-year disease-free interval, with similar rates of neurotoxicity and treatment-related mortality.

Because the overall survival for the high-dose arm in the SWOG trial (high-dose Ara-C induction and 2 cycles of high-dose Ara-C consolidation) is comparable to the CALGB trial with standard-dose infusional Ara-C induction and 4 cycles of high-dose Ara-C consolidation, the use of high-dose Ara-C in induction outside a clinical trial remains controversial. The decision to use high-dose Ara-C versus standard-dose Ara-C for induction might be influenced by consolidation strategies; fewer high-dose consolidation cycles may be needed for patients induced with high-dose Ara-C or for patients who will undergo early autologous stem cell transplantation. Although the remission rates are the same for standard- and high-dose Ara-C, 2 studies have shown more rapid marrow blast clearance after 1 cycle of high-dose therapy and a disease-free survival advantage for patients aged 50 years or younger who received the high-dose therapy.\textsuperscript{55} No data are available for doses of more than 60 mg of daunorubicin or 12 mg of idarubicin with high-dose Ara-C. High-dose Ara-C plus an anthracycline as induction therapy is considered a category 2B recommendation for patients younger than 60 years.

With either high- or standard-dose Ara-C-based induction for younger patients, between 20% and 45% of these patients will not experience remission. In a recent report of 122 patients treated with high-dose Ara-C and daunorubicin, the remission rates were strongly influenced by cytogenetics, with complete remission rates of 87%, 79%, and 62% for favorable-, intermediate-, and poor-risk groups, respectively.\textsuperscript{56}

Patients with antecedent hematologic disease or treatment-related secondary leukemia are considered poor-risk unless they have favorable cytogenetics, such as t(8;21), inv(16), t(16;16), or t(15;17). In addition, patients with unfavorable karyotypes such as −7, −5, 11q23 abnormalities or complex cytogenetic abnormalities are also considered poor-risk and treated similarly. This group of patients should be enrolled in a clinical trial (incorporating either chemotherapy or low-intensity therapy), if available, because only 40% to 50% of these patients experience complete remission with standard induction therapy, and response durations are short. In addition, HLA testing should be performed promptly in those who may be candidates for either fully ablative or reduced-intensity allogeneic HSCT from a sibling or an unrelated donor, which constitutes the best option for long-term disease control. Because patients...
with antecedent myelodysplasia or treatment-related leukemia have a decreased probability of experiencing remission through induction chemotherapy, transplantation without induction chemotherapy may be considered for those who have an available sibling donor and a relatively low percentage marrow involvement. In an EBMT (European Blood and Marrow Transplantation) trial, patients with high-risk myelodysplasia or AML evolving from myelodysplasia who underwent allogeneic transplantation without prior Ara-C–based chemotherapy had a 34% 3-year disease-free survival rate. Patients who underwent antecedent chemotherapy and experienced a complete remission had a 45% disease-free survival rate, compared with 10% for patients whose disease did not respond to chemotherapy before transplantation. An alternative strategy for patients with antecedent myelodysplasia who have not received a hypomethylating agent would be a trial of either decitabine or azacytidine while a rapid donor search is initiated.

**Postinduction Therapy:** To judge the efficacy of the induction therapy, a bone marrow aspirate and biopsy should be performed 7 to 10 days after completion of induction therapy. In patients who have received standard-dose Ara-C induction and have residual blasts without hypoplasia, additional therapy with standard-dose Ara-C and anthracycline should be considered. For those with significant residual blasts or clear-cut induction failure, escalation to high-dose Ara-C with or without an anthracycline is the most common salvage strategy. Other options include an allogeneic HSCT if a matched sibling or an alternative donor has been identified, or participation in a clinical trial. For patients whose clinical condition has deteriorated to the point that active treatment is no longer appropriate, best supportive care should be continued. If the marrow is hypoplastic (defined as cellularity < 10%–20% and residual blasts < 5%–10%), additional treatment selection may be deferred until marrow recovery when the remission status can be assessed.

Patients initially treated with high-dose Ara-C and who have significant residual blasts 7 to 10 days after completion of chemotherapy are considered to have induction failure. Additional high-dose Ara-C is unlikely to induce remission. If a sibling or HLA-matched unrelated donor has been identified, an allogeneic HSCT may salvage 25% to 30% of patients with induction failure. If no donor is immediately available, patients should be considered for a clinical trial.

 Occasionally, ALL therapy may be effective in patients with both myeloid and lymphoid markers at diagnosis (biphenotypic leukemia) if an AML induction regimen failed. Treatment decisions for patients with significant reduction without hypoplasia or those with hypoplasia are deferred until the blood counts recover and a repeat marrow is performed to document remission status. Response is then categorized as complete response or induction failure.

**Postremission or Consolidation Therapy:** Although successful induction therapy clears the visible signs of leukemia in the marrow and restores normal hematopoiesis in patients with de novo AML, additional therapy (consolidation) is needed to first reduce the residual abnormal cells to a level that can be contained by immune surveillance.

Since 1994, multiple (3–4) cycles of high-dose Ara-C therapy have been the nonprotocol standard consolidation regimen for patients younger than 60 years with either good- or intermediate-risk cytogenetics. This therapy is based on a CALGB trial comparing 100 mg/m², 400 mg/m², and 3 g/m² doses. The 4-year disease-free survival rate for patients receiving 3 g/m² was 44%, with a 5% treatment-related mortality rate and a 12% incidence of severe neurologic toxicity. Although the initial report did not breakdown disease-free survival rates according to cytogenetic subgroups, subsequent analysis showed disease-free survival rates of 60%, 30%, and 12% for good-, intermediate-, and poor-risk cytogenetics, respectively, in patients treated with high-dose Ara-C consolidation. These outcomes are similar to those seen in the high-dose Ara-C treatment arm of the SWOG trial, in which patients received high-dose Ara-C induction and 2 cycles of high-dose Ara-C consolidation. The CALGB trial also included maintenance chemotherapy after consolidation; however, only a small fraction of patients received maintenance, and subsequent trials have not included this aspect.

Other options for consolidation strategies include one or more cycles of high-dose Ara-C followed by autologous HSCT or allogeneic HSCT from sibling or unrelated donors. When choosing among these options, decisions are influenced by the 1) expected relapse rate with high-dose Ara-C
consolidation chemotherapy, 2) the additional morbidity and mortality associated with the transplant procedure, which in turn are strongly influenced by patient-specific comorbidity, and 3) salvage options. Factors such as patient age, comorbid conditions, and features of the disease at diagnosis, including elevated leukocyte counts (≥ 50,000/mcL) or number of cycles of induction to achieve remission, should play a role in choosing a consolidation strategy, as should issues regarding fertility and salvage options. Patients in whom 2 cycles of chemotherapy are required before remission are at very high risk for relapse and should be considered for either clinical trial or allogeneic transplant as initial consolidation whenever possible.

Previous guidelines have used cytogenetics as the major defining criteria for risk of relapse. This version of the NCCN Guidelines attempts to incorporate emerging data on the influence of mutations in specific genes, such as c-KIT, FLT3, CEBPA, and NPM1, on subsets of patients within a cytogenetic category. When the data on the CALGB trial was analyzed by cytogenetic groups, the dose-intensive Ara-C consolidation produced relapse-free survival rates of 50% to 60% overall in patients with inv(16) or t(8;21), with cumulative treatment-related mortality rates of 8% to 10%. The data were subsequently reanalyzed to include information on the effects of c-KIT mutations, which occur in 20% to 30% of these favorable-risk patients, on relapse rates and outcomes. In patients with inv(16), the relapse rate increased from 29% for wild-type c-KIT to 56% for patients with c-KIT mutations, which also translated into a decreased overall survival at 2 years of 56% versus 76%. In patients with t(8;21), the risk of relapse increased from 30% to 70% and the overall survival decreased to 42% at 2 years.

In the EORTC/GIMEMA trial comparing autologous and allogeneic HSCT, disease-free survival rates for patients with good-risk cytogenetics (t(8;21) or inv(16)) were 66% and 62%, respectively. Treatment-related mortality rates were 6% and 17%, respectively. Small single-institution studies have reported a disease-free survival rate of 88% for patients undergoing autologous HSCT. These data suggest that in this subgroup of patients with AML, allogeneic HSCT may be restricted to salvage therapy or those with c-KIT mutations.

Therefore, the panel recommends consolidation therapy for patients with better-risk cytogenetics involve either 3 to 4 cycles of high-dose Ara-C (category 1) followed by maintenance therapy (category 2B), or 1 to 2 cycles of dose-intensive Ara-C followed by autologous HSCT (category 2B) for patients with core binding factor leukemia lacking a c-KIT mutation. However, patients who have c-KIT mutations have a more similar outcome to those with intermediate-risk karyotype and should be considered for either clinical trials targeted toward the molecular abnormality, or consolidation strategies similar to those used in the intermediate-risk group. A carefully considered salvage plan with either sibling or unrelated donor HSCT should be an important part of the decision for these patients.

Panel members agreed that transplant-based options (either matched sibling or alternate donor HSCT, or 1 to 2 cycles of dose-intensive Ara-C followed by autologous stem cell transplantation) afforded a lesser risk of relapse and a somewhat higher disease-free survival compared with consolidation for most patients with intermediate-risk cytogenetics. In the EORTC/GIMEMA trial, the 4-year disease-free survival rates were 48.5% for allogeneic and 45% for autologous HSCT in patients with normal cytogenetics (with NN and –Y only). Other options for this group include clinical trials or multiple courses (3–4) of high-dose Ara-C consolidation. Alternative regimens incorporating intermediate doses of Ara-C (1.5–2.0 g/m²) are also acceptable in this group. Comparable 5-year disease-free survival rates were reported in patients younger than 60 years with normal karyotype after either 4 cycles of intermediate- or high-dose Ara-C (41%) or autologous HSCT (45%).

However, in the past 3 to 5 years, experts have learned that “normal” cytogenetics encompasses several molecular mutations with divergent risk behaviors. A large German trial showed additional molecular prognostic markers for patients with “normal” karyotype. The presence of an isolated mutant NPM1 cytoplasmic shuttle protein improves prognosis to a level comparable to that of patients with better-risk cytogenetics. For this subset of patients, therapy with multiple cycles of high-dose Ara-C is a reasonable option, and transplantation should be reserved until relapse. In contrast, patients with an isolated FLT3-ITD mutation and normal karyotype have a similar...
outlook to those with poor-risk cytogenetics\textsuperscript{14} and should be considered for a clinical trial or early allogeneic transplantation. Preliminary trials incorporating FLT3 inhibitors have been disappointing. The panel strongly recommends clinical trials as standard therapy for patients with poor prognostic features, which include FLT3 abnormalities in the setting of otherwise normal karyotype, high WBC count (> 50,000/mcL) at diagnosis, or 2 cycles of induction therapy needed to produce complete remission.

Sibling allogeneic HSCT produced a 43% disease-free survival rate in a group of patients with poor-risk cytogenetics in the EORTC/GIMEMA trial, with the International Bone Marrow Transplant Registry reporting similar outcomes for unrelated donor recipients. The outcome for autologous HSCT was comparable to chemotherapy, with an 18% disease-free survival rate.\textsuperscript{58} The panel uniformly endorsed allogeneic sibling HSCT or HLA-matched unrelated donors (including cord blood) or clinical trial as consolidation therapy for patients with poor-risk cytogenetics or molecular abnormalities, or those with therapy-related AML or prior myelodysplasia. Another option for this group is 1 to 2 cycles of high-dose Ara-C–based consolidation followed by autologous HSCT if no allogeneic transplant option is available (category 2B).

**Patients Aged 60 Years and Older**

**Induction Therapy:** The creation of separate algorithms for patients older than 60 years recognizes the poor outcomes seen with standard Ara-C and an anthracycline, particularly in those aged 75 years or older, or those aged 60 to 75 years with significant comorbidities or an ECOG performance status greater than 2.\textsuperscript{47,51} Treatment-related mortality frequently exceeds any expected transient response in this group. The British MRC AML 14 trial randomized 217 older patients unfit for chemotherapy to receive either 20 mg of Ara-C through subcutaneous injection twice daily for 10 consecutive days each month, or hydroxyurea.\textsuperscript{61} Ara-C produced a complete remission in 18% of the patients and a survival benefit in those with favorable or normal karyotype. Even this “low-intensity” approach had a 30-day mortality rate of 26%.

Most patients with leukemia seen by hematologists and oncologists consist of the “robust” baby boomers aged 60 to 75 years. Many of these patients will present with pancytopenia with modest marrow infiltration (20%–40%). If they are clinically stable, their cytogenetic prognostic group is helpful to know when deciding treatment.\textsuperscript{62}

For older patients (> 60 years) with AML, the panel recommends using performance status, adverse features (e.g., unfavorable cytogenetics and therapy-related AML or prior MDS), and comorbid conditions when selecting treatment, rather than age alone.

Older adults with good functional status (ECOG score 0–2), minimal comorbidity, and good-risk cytogenetic or molecular mutations, may benefit from standard therapies regardless of age. A reasonable treatment regimen for these patients is 7 days of continuous infusion standard-dose Ara-C (100–200 mg/m\textsuperscript{2}/d) along with 3 days of anthracycline. Patients older than 75 years with significant comorbidities usually do not benefit from conventional chemotherapy treatment. However, the rare patient with good or normal karyotype and no significant comorbidities may benefit from conventional chemotherapy treatment. For patients with normal karyotype, the remission rates are 40% to 50% with Ara-C combined with idarubicin, daunorubicin, or mitoxantrone. The study by Pautas et al.\textsuperscript{69} published as a 2007 ASH Annual Meeting abstract showed that idarubicin treatment, compared with high doses of daunorubicin up to 80 mg/m\textsuperscript{2}, yields higher complete response rates and more complete responses after one course. Löwenberg et al.\textsuperscript{61} showed that the complete remission rates and 2-year overall survival in patients between 60 and 65 years of age treated with daunorubicin, 90 mg/m\textsuperscript{2}, are also comparable to outcomes in patients treated with idarubicin (12 mg/m\textsuperscript{2}).\textsuperscript{64} and that the benefit in overall survival in the high-dose daunorubicin group was observed only in patients younger than 65 years and those with core binding factor leukemia.\textsuperscript{63}

Several promising therapeutic leads have emerged for the treatment of elderly patients with AML deemed unfit to undergo intensive chemotherapy.

The study by Burnett et al.\textsuperscript{61} established low-dose Ara-C as an accepted standard of care in elderly patients with AML who are unfit for chemotherapy. The study showed that low-dose Ara-C therapy was associated with a higher complete remission rate (18% vs. 1%) and longer overall survival compared with hydroxyurea.

Fenaux et al.\textsuperscript{65} compared 5-azacytidine with conventional care (e.g., best supportive care, low-dose...
Ara-C, intensive chemotherapy) in a study evaluating treatment options in patients with high-risk MDS using FAB criteria. However, using the 2008 WHO classification, 113 study patients (32%) fulfilled criteria for AML with a percentage of marrow blasts between 20% and 30%. In the subgroup of patients with RAEB-T, a significant survival benefit was seen with 5-azacytidine compared with best supportive care or low-dose Ara-C, which was exceeded by 9.5 months in both groups. A better overall survival was also seen with 5-azacytidine compared with standard induction therapy, but the difference was not significant because of small sample size.

Decitabine (20 mg/m²/d for 5 days) has been used as remission induction therapy for older patients with AML. The complete remission rate was 29% (including 3 of 10 patients with poor-risk cytogenetics). Both azacytidine and decitabine are approved by the FDA as therapy for myelodysplasia. The purine nucleoside analog clofarabine, which was approved by the FDA for relapsed pediatric ALL, has also received recent attention as a possible induction therapy for older patients. Results of a single-agent phase II trial showed that single-agent clofarabine was associated with an overall remission rate of 45%, with a 30-day mortality of 10%. In a group of 115 patients with a median age of 71 years, median overall survival was 59 weeks for responders versus 41 weeks for nonresponders. Confirmatory phase III trials are in progress for clofarabine.

The panel has included subcutaneous Ara-C, 5-azacytidine, and decitabine as low-intensity treatment options, and clofarabine as an intermediate-intensity treatment option for patients with AML aged 60 years or older. Best supportive care includes red cell and platelet transfusions to alleviate symptoms of anemia and thrombocytopenia; prophylactic antibiotic and antifungal drugs to reduce the risk of infection; and hydroxyurea for management of leukocytosis.

Older adults with newly diagnosed AML with an ECOG score between 0 and 2 with or without adverse features (e.g., therapy-related AML/prior MDS or unfavorable cytogenic or molecular markers) may be managed through either enrollment in a clinical trial, treatment with standard infusional Ara-C and anthracycline, or low-/intermediate-intensity therapy. Patients with an ECOG score greater than 2, significant comorbidity, or poor-risk cytogenetics are more likely to experience toxicity and less likely to benefit from standard induction chemotherapy. Therefore, the panel believes it is reasonable to offer these poor-risk patients either supportive care or enrollment in a clinical trial investigating novel agents or low-intensity therapy.

Postinduction Therapy: Similar to younger patients, older patients who undergo standard Ara-C/anthracycline induction therapy are evaluated with a bone marrow analysis 7 to 10 days after completion of chemotherapy, and categorized according to the presence of blasts or hypoplasia. Patients with significant cytoreduction without hypoplasia may receive standard-dose Ara-C with an anthracycline or anthracyclenedione. A repeat bone marrow analysis is performed in these patients and those with hypoplasia after induction to document the remission status. Because many older patients have some evidence of antecedent myelodysplasia, full normalization of peripheral blood counts often does not occur even if therapy clears the marrow blasts. Thus many phase I/II trials for AML in older patients include categories such as incomplete complete remission (CRi) for patients who have fewer than 5% marrow blasts but have mild residual cytopenia.

Many of the newer treatment strategies are designed to work more gradually, using agents that may allow expression of tumor suppressor genes (e.g., a methyltransferase inhibitor such as decitabine or 5-azacytidine) or through increasing apoptosis (e.g., histone deacetylators). Thus, success in these trials may be assessed using indirect measures such as hematologic improvement or decreased transfusion requirements, and survival without actually experiencing complete remission. In these trials, marrow examination frequently is not performed until completion of 1 or 2 cycles of therapy.

Patients who experience a complete remission (including CRi) with standard induction chemotherapy may receive further consolidation with these agents. The French Acute Leukemia (ALFA) 98 trial randomized patients experiencing remission to consolidation with either one additional course of standard Ara-C, 200 mg/m², for 7 days plus the anthracycline to which they had been randomized for induction (idarubicin, 9 mg/m², for 4 days, or daunorubicin, 45 mg/m², for 4 days) or 6 monthly courses at 1 day of anthracycline at the above doses and Ara-C, 60 mg/m², every 12 hours as a subcutaneous
infusion at home for 5 days each month. Patients in the ambulatory arm had a better 2-year disease-free survival rate (28%) than those in the single intense consolidation arm (17%; \( P = .03 \)). Overall survival, transfusion requirement, and days in hospital all favored the ambulatory arm.\(^{68} \)

Although the CALGB trial did not show an overall benefit for higher doses of Ara-C consolidation in older patients, a subset of patients with a good performance status, normal renal function, and a normal or low-risk karyotype might be considered for a single cycle of Ara-C (1.0–1.5 g/m\(^2\)/d for 4–6 doses) without an anthracycline.

The role of myeloablative allogeneic HSCT is limited in older patients because of significant comorbidities, but interest in reduced-intensity allogeneic HSCT as consolidation therapy continues.\(^{69,70} \)

Case series and analysis of registry data have reported encouraging results, with 2-year overall survival rates of 40% to 60% and a nonrelapse mortality rate of 20% for patients undergoing transplant in remission. However, Estey et al.\(^{71} \) prospectively evaluated a protocol in which patients older than 50 years with unfavorable cytogenetics would be assessed for a reduced-intensity allogeneic HSCT. Of the 259 initial patients, only 14 ultimately underwent transplantation, because of illness, lack of donor, refusal, or unspecified reasons. The authors compared the results with matched cases receiving conventional-dose chemotherapy. Results suggested that reduced-intensity allogeneic HSCT was associated with improved relapse-free survival, and the authors concluded that this approach remains of interest. For this strategy to be better used, potential candidacy should be considered during induction, and unrelated donor options explored early.

The guidelines note that reduced-intensity allogeneic HSCT is considered an additional option for patients aged 60 years and older either as a postremission therapy for those experiencing a complete response to induction therapy or to treat induction failure only in patients with low-volume disease.

**Postremission Surveillance and Salvage Therapy**

CBC counts, including platelets, should be monitored every 1 to 3 months for the first 2 years after patients have completed consolidation, then every 3 to 6 months for a total of 5 years. Bone marrow evaluation is recommended only if the hemogram becomes abnormal, rather than as routine surveillance at fixed intervals, unless it is part of a research protocol.

A matched unrelated donor search (including cord blood) should be initiated for high-risk patients experiencing first complete remission who would be candidates for HSCT, or be considered concomitant with initiation of reinduction therapy during first relapse in appropriate patients.

Treatment strategies for relapse are categorized according to patient age. For patients younger than 60 years who have experienced a relapse, enrollment in a clinical trial is considered appropriate and is strongly preferred by the panel. If the relapse occurs after a “long” (>12 months) remission, retreatment with the previously successful regimen is an option. If the relapse is detected when the tumor burden is low and the patient has a previously identified sibling or unrelated donor, salvage chemotherapy followed by allogeneic HSCT can be considered. Transplant should be considered only if the patient has experienced remission or in the context of a clinical trial.

The algorithm provides a list of some commonly used salvage regimens (page 298). The regimens included represent purine analog (e.g., fludarabine, cladribine) regimens that have shown remission rates of 30% to 40% in several clinical trials and those that have been used in the comparator arms in U.S. cooperative group trials in the past decade. The representative regimens include 1) cladribine, Ara-C, and granulocyte colony-stimulating factor (G-CSF) with or without mitoxantrone or idarubicin; 2) fludarabine, Ara-C, G-CSF with or without idarubicin; and 3) mitoxantrone, etoposide, and Ara-C (MEC).

Patients aged 60 years or older who are robust and wish to pursue treatment after relapse may be offered 1) therapy on clinical trial (strongly preferred option by the panel); 2) salvage chemotherapy followed by match sibling or alternate donor HSCT (transplant should be considered only if the patient has experienced remission or in the context of a clinical trial); or 3) repetition of the initial successful induction therapy only if they had a long initial remission (i.e., relapse >12 months of induction therapy). Best supportive care is always an option for those who do not wish to pursue intensive treatment.

**Supportive Care**

Based on results of an ECOG study, growth-factor support may be considered for older patients after chemotherapy administration.\(^{77} \) Recommendations on the use of cytokines for infection or slow marrow...
recovery is left to institutional policy. G-CSF should be discontinued for a minimum 7 days before assessing marrow because it may affect interpretation of pathology.

Leukocyte-depleted blood products should be used for transfusion. Cytomegalovirus (CMV) screening for potential HSCT candidates is left to institutional policies regarding provision of CMV-negative blood products to patients who are CMV-negative at diagnosis. Radiation of all blood products is advised to reduce the risk of graft-versus-host disease in all immunosuppressed patients.

Standard tumor lysis prophylaxis is hydration with alkalinization of the urine, allopurinol administration, or rasburicase treatment. Rasburicase is a genetically engineered recombinant form of urate oxidase enzyme, and should be considered as initial treatment in patients with rapidly increasing blast counts, high uric acid, or evidence of impaired renal function.

Patients who receive high-dose Ara-C must be closely monitored for changes in renal function. Renal dysfunction is highly correlated with increased risk of cerebellar toxicity. Patients must be monitored for nystagmus, dysmetria, and ataxia before each dose of high-dose Ara-C; patients exhibiting any neurologic signs should discontinue high-dose Ara-C, and all subsequent Ara-C therapy must be standard-dose. Patients who develop cerebellar toxicity should not be rechallenged with high-dose Ara-C in future treatment cycles. High-dose Ara-C induction therapy may substitute for intrathecal chemotherapy because it crosses the blood–brain barrier. The cerebrospinal fluid must then be reassessed after induction and further therapy given as appropriate. Intrathecal use of liposomal Ara-C, which has a longer half-life, offers the benefit of less-frequent (once weekly) administration.

If the initial CT/MRI identifies a mass effect or increased intracranial pressure, a needle aspiration or biopsy should be considered. If positive, radiation therapy should be considered strongly followed by intrathecal therapy. Intrathecal therapy or high-dose Ara-C should not be administered concurrently with cranial radiation because of increased risks of neurotoxicity.

The panel does not recommend routine screening for occult CNS disease in most patients with AML in remission, except for those with M4 or M5 morphology, biphenotypic leukemia, or WBC counts greater than 100,000/mcL at diagnosis. For patients with positive cytology, the panel recommends either intrathecal chemotherapy or documenting clearance of CNS disease after the first cycle of high-dose Ara-C chemotherapy. In addition to the recommended evaluation and treatment of CNS leukemia, further CNS surveillance is recommended based on institutional practice.

**Evaluation and Treatment of CNS Leukemia**

Leptomeningeal involvement is much less frequent (< 3%) in AML than in ALL; therefore, the panel does not recommend lumbar punctures during routine diagnostic workup. However, if neurologic symptoms are present at diagnosis, such as headache, confusion, or altered sensorium, an initial CT/MRI should be performed to rule out a bleed or mass effect. If no mass effect is found, cerebrospinal fluid cytology should be sampled with lumbar puncture. If the lumbar puncture is negative, the procedure can be repeated if symptoms persist. If the lumbar puncture is positive, intrathecal chemotherapy with Ara-C or methotrexate is recommended concurrent with systemic induction therapy. Initially, the intrathecal therapy is given twice a week until the cytology shows no blasts, and then weekly for 4 to 6 weeks. High-dose Ara-C induction therapy may substitute for intrathecal chemotherapy because it crosses the blood–brain barrier. The cerebrospinal fluid must then be reassessed after induction and further therapy given as appropriate. Intrathecal use of liposomal Ara-C, which has a longer half-life, offers the benefit of less-frequent (once weekly) administration.

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## Individual Disclosures of the NCCN Acute Myeloid Leukemia Panel

<table>
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The NCCN guidelines staff have no conflicts to disclose.