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These guidelines are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no representations nor warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way. These guidelines are copyrighted by National Comprehensive Cancer Network. All rights reserved. These guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2007
Summary of changes in the 1.2008 version of the Acute Myeloid Leukemia guidelines from the 2.2007 version include:

**AML-2**
- Low/intermediate APL patients were defined as having a white blood cell count < 10,000/mcL in footnote "m", based on the prognostic index reported by the PETHEMA group (Sanz et al).
- The dose of cytarabine used for APL consolidation was clarified as an intermediate dose of ≥ 1 g/m² in footnote "t".
- The use of 1-2 weeks of ATRA as a component of anthracycline-based consolidation of APL is now recommended rather than suggested.
- An important caveat of all three successful APL regimens (PETHEMA, French, or US Intergroup) is that in order to achieve the results expected with that regimen, one needs to follow all aspects of the regimen and not mix induction from one with consolidation from another.
- If a patient initially treated with ATRA + arsenic, consolidation therapy is recommended for 6 cycles (previously 2-3).

**AML-3**
- Footnote "u" recommends that molecular monitoring be done in a laboratory with experience in PCR technology and sufficient volume to maintain consistent accurate sensitivity.

**AML-4**
- Gemtuzumab was added as an option for postremission therapy for patients with early relapse post arsenic therapy.
- Arsenic consolidation is recommended for a total of 6 cycles.

**AML-5**
- Footnote "aa" was added describing the additional factors that should be considered in determining patients able to tolerate conventional induction therapy. These include patients with poor PS and comorbidities.
- The dose of standard-dose cytarabine was clarified as 100-200 mg/m². The dose of high-dose cytarabine was clarified as 2-3 g/m².
- The recommendation for mitoxantrone in combination with cytarabine was deleted for younger patients (< 60 y).

**AML-6**
- The recommendation for mitoxantrone in combination with cytarabine was deleted for younger patients (< 60 y).

**AML-9**
- The dose of standard-dose cytarabine was clarified as 100-200 mg/m².

**AML-10**
- The dose of standard-dose cytarabine was clarified as 100-200 mg/m².

**AML-A**
- Footnote 2 is new to the page.

**AML-B**
- Molecular mutations (c-KIT, FLT3 and NPM1) have been added as modifying risk factors for patients with t(8;21), inv(16) or normal karyotype.
**DIAGNOSIS**

Acute leukemia\(^a,b,c\) or chloroma

**WORKUP**

- H&P
- CBC, platelets, differential, chemistry profile
- PT, PTT, fibrinogen
- Bone marrow with cytogenetics (mandatory)
- Immunophenotyping or cytochemistry\(^d\)
- HLA typing (in patients considered potential HSCT candidates)\(^e\)
- Cardiac scan if prior cardiac history or prior anthracycline use or clinical symptoms which would raise concern about cardiac function
- Central venous access of choice
- Consider evaluation for c-KIT, FLT3\(^f\), and NPM\(^1\) mutations\(^g\)
  - If clinically indicated:
    - Begin alternative donor search if patient has therapy-related AML, an antecedent hematologic disorder, or known poor-risk cytogenetics\(^h\) and there is no sibling donor
    - Lumbar puncture (LP), if symptomatic\(^i\)
      - (category 2B for asymptomatic)

**CLASSIFICATION/STAIN ANALYSIS**

- Immunophenotyping (+) for
  - \(\geq 2\) myeloid markers and (+) for typically < 2 lymphoid markers\(^j\)
  - or
  - Myeloperoxidase (+)
  - or
  - Nonspecific esterase (+)
  - or
  - Butyrate esterase (+)

- Myeloperoxidase (–)
- Nonspecific esterase (–)

- TdT (+)
  - or
  - Immunophenotyping (+) for
    - \(\geq 2\) lymphoid markers and (+) for < 2 myeloid markers\(^j\)
    - TdT (+)

**Acute promyelocytic leukemia (APL)**

See Treatment Induction (AML-2)

**Acute myeloid leukemia (AML)**

See Treatment Induction (AML-5)

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

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\(^a\)The WHO classification defines acute leukemia as \(\geq 20\%\) blasts in the marrow or blood.

\(^b\)Ongoing clinical trials for AML and high-risk MDS may continue to use FAB criteria of \(\geq 30\%\) 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.

\(^c\)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 there is the advantages of clinical trials.

\(^d\)Rare patients who present with extramedullary disease (chloroma) should be treated with systemic therapy. Local therapy (surgery/RT) may be used for residual disease.

\(^e\)Testing for FLT3, c-KIT and NPM\(^1\) mutations are not commonly available in the community. Consider having an additional aliquot of marrow from the pre-treatment sample frozen for testing at a later point if it becomes relevant for risk analysis after classic cytogenetics results are available.

\(^f\)May be useful in clinical trials and prognosis.

\(^g\)For risk status based on cytogenetics and molecular mutations, see AML-B.

\(^h\)For patients with major neurologic signs or symptoms at diagnosis, appropriate imaging studies should be performed to detect meningeal disease, chloromas, or CNS bleeding. LP should be performed if no mass/lesion detected on imaging study. Screening LP should be considered at first remission for patients with M5 or M4 morphology or WBC > 100,000/mcL at diagnosis. See Evaluation and Treatment of CNS leukemia (AML-A).

\(^i\)When presented with rare cases not fitting this algorithm, consultation with an experienced hematopathologist is recommended.

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Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
### APL

#### CLASSIFICATION

<table>
<thead>
<tr>
<th>M3 morphology and (+) for t(15;17) by either cytogenetics or molecular testing; consider possibility of M3 variant</th>
</tr>
</thead>
</table>

#### TREATMENT INDUCTION

<table>
<thead>
<tr>
<th>Induction Failure</th>
<th>Complete Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATRA + arsenic trioxide or Matched sibling or alternative donor HSCT</td>
<td>ATRA + arsenic trioxide x 6 cycles</td>
</tr>
</tbody>
</table>

#### CONSOLIDATION THERAPY

Consolidate with at least 2 cycles of anthracycline-based (idarubicin or daunorubicin) chemotherapy + 1-2 wk ATRA with each cycle (based on risk status)^5,t (category 1)

- Arsenic trioxide
- Matched sibling or alternative donor HSCT

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^k Three 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.

^l In patients with clinical and pathologic features of APL, it is preferable to start ATRA early and if t(15;17) not confirmed, discontinue ATRA and continue treatment as for AML.


^n Monitor for APL differentiation syndrome and disseminated intravascular coagulation (DIC), see Supportive Care (AML-C 2 of 2).

^o See Arsenic trioxide monitoring, Supportive Care (AML-C 2 of 2).


^q Earlier assessment may be misleading. Patients are often still molecularly positive at the end of induction.

^r See Response Criteria for Acute Myeloid Leukemia (AML-D).


^t In some trials, the addition of at least the intermediate dose of cytarabine (> 1 g/m²) or arsenic trioxide have shown improvement in relapse-free survival. The benefit to cytarabine seems to be in high risk patients.

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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.
Polymerase chain reaction (PCR) should be performed on a marrow sample at completion of consolidation to document molecular remission. Prior practice guidelines have recommended monitoring marrow or peripheral blood PCR every 3 mo for 2 y to detect molecular relapse. We continue to endorse this for high risk patients, those over age 60 y or who had long interruptions during consolidation. Clinical experience indicates that risk of relapse in patients with low risk disease who are in molecular remission at completion of consolidation is uncommon and 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 by peripheral blood or bone marrow in a reliable laboratory with appropriate technology and experience 4 wks later and if molecular relapse is confirmed by a second positive test, intervention should be strongly considered (eg, 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 negative. Testing should be done in the same lab to maintain level of sensitivity.

If patient confirmed molecularly positive, treat as relapse (AML-4).

There are data that ATRA ± 6-mercaptopurine + methotrexate improve disease-free survival, but confirmatory studies are still in progress. However much of the data for ATRA maintenance ante dated the addition of ATRA to consolidation.
**Acute Myeloid Leukemia**

**APL**

**POSTREMISSION THERAPY**

- First relapse
- Arsenic trioxide
- Gemtuzumab ozogamicin (if early relapse post arsenic therapy)

**ADDITIONAL THERAPY**

- PCR negative
  - Second remission (morphologic)
  - Matched or alternative donor HSCT
  - Clinical trial
  - Gemtuzumab ozogamicin

- PCR positive
  - No remission
  - Autologous HSCT
  - Arsenic consolidation (total of 6 cycles) (if not a transplant candidate)

- Clinical trial

**Note:** All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.


*At the end of 2 cycles, if patient is not in molecular remission, consider matched sibling or alternative donor HSCT or clinical trial.*
**CLASSIFICATION**

- **No antecedent hematologic disease**
  - Age < 60 y
  - Age ≥ 60 y

- **Antecedent hematologic disease**
  - Age < 60 y
  - Age ≥ 60 y

- **Antecedent hematologic disease or treatment-related AML**

**TREATMENT INDUCTION**

- **Standard-dose cytarabine (100-200 mg/m² continuous infusion (CI) x 7 days) with anthracycline (idarubicin or daunorubicin) x 3 days (may require 2 cycles) (category 1)** or **High-dose cytarabine 2-3 g/m² (HiDAC) with anthracycline (idarubicin or daunorubicin) (1 cycle) (category 2B)**

- **Clinical trial (incorporating either chemotherapy or low-intensity therapy)** or **Matched or alternative donor HSCT (category 2B)**

**See Post-induction Therapy (AML-6)**

**See Post-induction Therapy (AML-7)**

**See Induction Therapy (AML-9)**

**Note:** All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

**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 there is the advantage of clinical trials.

**x** See Supportive Care (AML-C).

**z** 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 to lower the white count to < 50,000/mcL. Prompt institution of definitive therapy is essential.

**aa** Poor performance status and comorbid medical condition, in addition to age are factors which influence ability to tolerate standard induction therapy (See AML-A).

**bb** Patients with known poor-prognosis karyotypes prior to treatment may be treated like patients with an antecedent hematologic disorder.

**cc** Rare patients with favorable karyotypes [inversion 16, t(8;21), t(16;16)] may be candidates for standard induction therapy, or APL therapy for t(15;17).

**dd** See Monitoring During Therapy (AML-E).

**ee** The use of high-dose cytarabine for induction outside the setting of a clinical trial is still controversial. While the remission rates are the same for standard- and high-dose cytarabine, two studies have shown a disease-free survival advantage for patients ≤ age 50 who received the high-dose therapy (category 2B).

**ff** The benefit of induction chemotherapy prior to allogeneic HSCT versus immediate HSCT is unclear in patients with high grade MDS and low blast count AML evolving from MDS. If donor is available, allogeneic HSCT without prior induction therapy is an option, particularly for patients with poor risk cytogenetics.
AML POST-INDUCTION THERAPY

AFTER STANDARD-DOSE CYTARABINE

Age < 60 y

- Significant residual blasts
- Follow-up bone marrow

- Standard-dose cytarabine with anthracycline (idarubicin or daunorubicin) or
- High-dose cytarabine
- See treatment for Induction failure

Hypoplasia

Await recovery

POSTREMISSION THERAPY

- Complete response
- Marrow to document remission status upon hematologic recovery

- Clinical trial
- Matched sibling or alternative donor HSCT
- 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

**Notes:**
- All recommendations are category 2A unless otherwise indicated.
- Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
- See Response Criteria for Acute Myeloid Leukemia (AML-D).
- See Supportive Care (AML-C).
- See Monitoring During Therapy (AML-E).
- Begin matched unrelated donor search if no appropriate sibling donor is available and patient is a candidate for an allogeneic HSCT.
- Hypoplasia is defined as cellularity < 10-20% and residual blasts < 5-10%.
- Patients in remission may be screened with LP if initial WBC > 100,000/mcL or monocytic histology. See Evaluation and Treatment of CNS leukemia (AML-A).
**Guidelines Index**

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**Practice Guidelines in Oncology – v.1.2008**

**AML POST-INDUCTION THERAPY**

* AFTER HIGH-DOSE CYTARABINE

Age < 60 y

- **Significant residual blasts**
  - **See treatment for Induction failure**

- **Significant cyto-reduction without hypoplasia**
  - **Await recovery**

  - **Hypoplasia**
    - **Await recovery**

- **Follow-up bone marrow**
  - **Significant cyto-reduction without hypoplasia**
    - **Await recovery**

- **Marrow to document remission status upon hematologic recovery**

- **Complete response**
  - **See Postremission Therapy (AML-8)**
  
- **Clinical trial or**
  - **Matched sibling or alternative donor HSCT or**
  - **Best supportive care**

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* See Response Criteria for Acute Myeloid Leukemia (AML-D).

x See Supportive Care (AML-C).

dd See Monitoring During Therapy (AML-E).

gg Begin matched unrelated donor search if no appropriate sibling donor is available and patient is a candidate for an allogeneic HSCT.

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

ii Patients in remission may be screened with LP if initial WBC > 100,000/mcL or monocytic histology. See Evaluation and Treatment of CNS leukemia (AML-A).

**Note:** All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
**POSTREMISSION THERAPY**

- **Better-risk cytogenetics**
  - High-dose cytarabine, $3 g/m^2$ over 3 h every 12 h on days 1, 3, 5 × 4 courses (category 1)
  - or
  - 1 to 2 cycles of high-dose cytarabine-based consolidation followed by autologous HSCT (category 2B)
  - or
  - Clinical trial

- **Intermediate-risk cytogenetics**
  - Matched sibling or autologous HSCT
  - or
  - High-dose cytarabine, $3 g/m^2$ over 3 h every 12 h on days 1, 3, 5 × 4 courses
  - or
  - Clinical trial

- **Antecedent hematologic disease, treatment-related disease or poor-risk cytogenetics**
  - Clinical trial
  - or
  - Matched sibling
  - or
  - Alternative donor HSCT

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**Note:** All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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- **Age < 60**
  - Better-risk cytogenetics
  - Intermediate-risk cytogenetics
  - Antecedent hematologic disease, treatment-related disease or poor-risk cytogenetics

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<table>
<thead>
<tr>
<th>g9</th>
<th>Begin matched unrelated donor search if no appropriate sibling donor is available and patient is a candidate for an allogeneic HSCT.</th>
</tr>
</thead>
<tbody>
<tr>
<td>ii</td>
<td>For risk status based on cytogenetics and molecular mutations, see AML-B.</td>
</tr>
<tr>
<td>kk</td>
<td>Isolated FLT3 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.</td>
</tr>
<tr>
<td>ll</td>
<td>Alternative regimens incorporating intermediate (1.5-2 gm) doses are acceptable.</td>
</tr>
<tr>
<td>mm</td>
<td>While the original study design incorporated maintenance chemotherapy following a planned 4 cycles of consolidation, only a small fraction of the patients who received HiDAC, also received maintenance therapy.</td>
</tr>
<tr>
<td>nn</td>
<td>While 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.</td>
</tr>
<tr>
<td>oo</td>
<td>Clinical trials when available are strongly recommended in the treatment of patients with poor prognostic features (e.g., high WBC, CD56+, or two cycles of induction needed to achieve CR).</td>
</tr>
<tr>
<td>pp</td>
<td>“Matched sibling” refers to a complete match or one antigen mismatch.</td>
</tr>
<tr>
<td>qq</td>
<td>Patients may require at least one cycle of high dose cytarabine consolidation while donor search is in progress.</td>
</tr>
</tbody>
</table>
Obtain cytogenetics prior to treatment when possible.

Complex cytogenetics

Low-intensity therapy or Best supportive care

Clinical trial or Low-intensity therapy or Best supportive care

Clinical trial (preferred)

Non-complex cytogenetics

Standard-dose cytarabine (100-200 mg/m² CI x 7 days) with anthracycline (idarubicin or daunorubicin) or mitoxantrone (7+3) (may require 2 cycles) (category 1)

Clinical trial or Low-intensity therapy or Best supportive care

See Post-induction Therapy (AML-10)

PS > 2 →

Age ≥ 60 - 75

PS ≤ 2 →

Complex cytogenetics

Obtain cytogenetics prior to treatment when possible

Non-complex cytogenetics

Clinical trial or Low-intensity therapy or Best supportive care

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

See Supportive Care (AML-C).

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 to lower the white count to < 50,000/mcL. Moreover, rapid institution of definitive therapy is essential.

See Monitoring During Therapy (AML-E).

Patients over 75 years old rarely benefit from conventional chemotherapy treatment. However, the rare patient with excellent performance status and good or normal karyotype may benefit from conventional chemotherapy treatment.

Most older patients have low peripheral blood WBC and slow proliferative rates. These patients can be treated with supportive care measures during the interval needed to obtain cytogenetics results.

Complex cytogenetics is defined as 3 or more abnormalities.
AML POST-INDUCTION THERAPYx,dd
AFTER STANDARD-DOSE CYTARABINE
Age ≥ 60 y

Follow-up bone marrow

Hypoplasia

Significant cytoreduction without hypoplasia

Significant residual blastsgg

See treatment for Induction failure or Supportive care

Standard-dose cytarabine with anthracycline (idarubicin or daunorubicin) or mitoxantrone or Reduced intensity matched sibling transplant, if donor available, on clinical trial

Complete responser,ii

Marrow to document remission status upon hematologic recovery

Induction failurer

Clinical trial or Reduced intensity HSCT in context of clinical trial or Standard-dose cytarabine (100-200 mg/m²/day x 5-7 d x 1-2 cycles) ± anthracycline (idarubicin or daunorubicin) or Consider cytarabine 1-1.5 g/m²/day x 4-6 doses x 1-2 cycles for patients with good performance status, normal renal function, good or normal karyotype.

Clinical trial or Reduced intensity HSCT in context of clinical trial or Best supportive care

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
**SURVEILLANCE**
(POST 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
- Matched unrelated donor search should be initiated at first relapse in appropriate patients concomitant with institution of other therapy if no sibling donor has been identified

**SALVAGE THERAPY**

- Early (< 6 mo)
  - Clinical trial or
  - Salvage chemotherapy followed by matched sibling or alternative donor HSCT

- Late (> 6 mo)
  - Clinical trial or
  - Salvage chemotherapy followed by matched sibling or alternative donor HSCT or
  - Repeat initial successful induction regimen

- Age < 60
  - Relapse
    - Early (< 6 mo)
      - Clinical trial or
      - Salvage chemotherapy followed by matched sibling or alternative donor HSCT
    - Late (> 6 mo)
      - Clinical trial (strongly preferred) or
      - Best supportive care or
      - Gemtuzumab ozogamicin

- Age ≥ 60
  - Early (< 6 mo)
    - Clinical trial (strongly preferred) or
    - Treatment with initial successful regimen or
    - Gemtuzumab ozogamicin or
    - Best supportive care

- Late (> 6 mo)

*See Response Criteria for Acute Myeloid Leukemia (AML-D).*

**PP** “Matched sibling” refers to a complete match or one antigen mismatch.

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

**VV** May include trials of reduced intensity/nonmyeloablative HSCT.

**Note:** All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
EVALUATION AND TREATMENT OF CNS LEUKEMIA

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, chloromas, or CNS bleeding. LP should be performed if no mass/lesion detected on imaging study. Screening LP should be considered at first remission for patients with M5 or M4 morphology or WBC > 100,000/mcL at diagnosis.
3 Induction chemotherapy should be started concurrently.
4 Concurrent use of CNS RT with high-dose cytarabine or IT methotrexate may increase risk of neurotoxicity.

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
## RISK STATUS BASED ON CYTOGENETICS AND MOLECULAR MUTATIONS

<table>
<thead>
<tr>
<th>RISK STATUS</th>
<th>CYTOGENETICS</th>
<th>MOLECULAR MUTATIONS</th>
</tr>
</thead>
</table>
| Better-risk   | Inv(16)<sup>1</sup>  
t(8;21)<sup>1</sup>  
t(16;16)<sup>1</sup> | Normal cytogenetics with isolated NPM<sub>1</sub> mutation |
| Intermediate-risk | Normal  
+8 only  
t(9;11)  
Other abnormalities not listed with better-risk and poor-risk cytogenetics and molecular mutations | c-KIT<sup>3</sup> in patients with t(8;21) or Inv(16) |
| Poor-risk     | Complex (≥ 3 abnormalities)  
-5  
-7  
5q-  
7q-  
Abnormalities of 11q23, excluding t(9;11)  
Inversion 3  
t(3;3)  
t(6;9)  
t(9;22)<sup>2</sup> | Normal cytogenetics with isolated FLT3 mutations |

<sup>1</sup>Other abnormalities in addition to these findings do not alter better risk status.

<sup>2</sup>Philadelphia+ AML t(9;22) consider managing as myeloid blast crisis in CML.  See NCCN Chronic Myelogenous Leukemia Guidelines.

<sup>3</sup>Emerging data indicates that the presence of c-KIT mutations in patients with t(8;21) and to a lesser extent Inv(16) confers a higher risk of relapse. These patients should be considered for clinical trials, if available.

Note: All recommendations are category 2A unless otherwise indicated.  Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
SUPPORTIVE CARE (1 of 2)

There are variations between institutions but the following issues are important to consider in the management of patients with AML.

General
- Prophylactic antibiotics, including antifungals, are left to the discretion of the individual institutions.
- Growth factors may be considered in the elderly after chemotherapy is complete. Note that such 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.
- 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 symptoms of anemia; platelets for patients with platelets < 10,000/mcL or with any signs of bleeding.¹
  - CMV screening for potential HSCT candidates may be considered.
- Tumor lysis prophylaxis: hydration with diuresis, and urine alkalinization and allopurinol.
- Clinical evidence of tumor lysis syndrome and problematic hyperuricemia or inability to tolerate oral medication: consider rasburicase.
- Saline or steroid eye drops to both eyes four times daily for all patients undergoing high-dose cytarabine therapy until 24 h post completion of cytarabine.
- Screening LP for occult CNS disease is a consideration for remission patients who had initial WBC > 100,000/mcL or monocytic histology.
- Patients receiving high dose cytarabine therapy (particularly those with impaired renal function or patients > 60 years), 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 due to tumor lysis, high-dose cytarabine should be discontinued until creatinine normalizes.

¹Patients who are allo-immunized should receive HLA-specific blood products.
SUPPORTIVE CARE (2 of 2)

**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 replace clotting factors. Monitor daily until coagulopathy resolves.
- **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 days with a taper over 2 wks). Consider interrupting ATRA therapy until hypoxia resolves.
- **Patients with relapsed APL or with hyperleukocytosis after ATRA may be at increased risk of CNS disease. Prophylactic intrathecal therapy (IT) is being evaluated in this group.**
- **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.**
- **Arsenic trioxide monitoring**
  - Prior to 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 millisec (weekly during induction therapy and before each course of post-remission therapy)

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1 Package insert for arsenic trioxide (www.trisenox.com)

**Note:** All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
## RESPONSE CRITERIA FOR ACUTE MYELOID LEUKEMIA

1. **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 one week.
   - A bone marrow biopsy should be performed if spicules are absent from the aspirate sample.
2. **Complete remission**
   - Patient achieves a morphologic leukemia-free state and
     - Absolute neutrophil count > 1000/mcL
     - Platelets ≥ 100,000/mcL
     - No residual evidence of extramedullary disease
     - Morphologic CR - patient independent of transfusions
     - Cytogenetic CR - cytogenetics normal (in those with previously abnormal cytogenetics)
     - Molecular CR - molecular studies negative
3. **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.
4. **Patients failing to achieve a complete response are considered treatment failures.**
5. **Relapse following 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 (eg, bone marrow regeneration after consolidation therapy) or extramedullary replase.**

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2. There are some clinical trials, particularly in the elderly or those with antecedent myelodysplasia, who are reporting a variant of CR referred to as CRp or CRi. This has been loosely defined as < 5% marrow blasts and transfusion independence but with persistence of cytopenia (usually thrombocytopenia). This is clinically relevant only in APL and Ph+ leukemia at the present time.
3. PR’s are only useful in assessing responsiveness to new agents and should not be considered a therapy goal for standard therapy.
MONITORING DURING THERAPY

**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 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.

**Post–remission 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 achieve a CR, are at increased risk for relapse and may be considered for early unrelated donor search, as indicated on AML-8
Overview

Approximately 13,410 people will be diagnosed with acute myeloid leukemia (AML) in 2007, and 8,990 patients will die from the disease. As the population ages, the incidence of AML, along with myelodysplasia, appears to be rising. Equally disturbing is the increasing incidence of treatment-related myelodysplasia and leukemia in survivors of tumors of childhood and young adulthood such as Hodgkin's disease, sarcomas, breast and testicular cancers, and lymphomas. Ionizing radiation and occupational exposure to benzene and petrochemicals are also associated with AML.

The clinicians comprising the NCCN AML panel convene 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 in acute promyelocytic leukemia (APL). However, recent large clinical trials have highlighted the need for new, innovative strategies since outcomes for AML patients, particularly the older patients, have not substantially changed in the last three decades.

The NCCN AML 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 include an effort to provide a rationale for the inclusion of several of the treatment options in some categories.

Initial Evaluation

The initial evaluation has two 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 may have an impact on chemo-responsiveness 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 information factors are taken into consideration for treatment decisions.

There are two systems commonly used by pathologists to define hematopoietic malignancies. The French-American-British (FAB) classification is based on morphology relying on cytochemical stains and also incorporates flow cytometry to define an immunophenotype which separates myeloid from lymphoid blasts. Acute myeloid leukemia is then subcategorized into eight entities based on degree of differentiation. The FAB classification (1976) sets the threshold between high-grade myelodysplasia (MDS) and AML at 30% blasts.

The 1999 World Health Organization (WHO) classification was designed to include newer prognostic factors such as molecular
markers, chromosome translocations, and evidence of dysplasia either by morphology or history which might predict biologic responsiveness, allowing 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 that indicated equivalently poor survival for MDS patients with 20-30% blasts as for AML patients with >30% blasts, the WHO lowered the threshold for the diagnosis of AML to >20% blasts and abolished the MDS category of refractory anemia with excess blasts in transformation (RAEBT). In addition, WHO allows the diagnosis of AML 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 for the Diagnosis and Standardization of Response Criteria accepted the cytochemical and immunophenotypic criteria of WHO as the standard for diagnosis of AML including the reporting of dysplasia by morphology. As yet, however, there is no evidence that dysplasia represents an independent risk factor as it is frequently linked to poor risk cytogenetics.

Based on the recommendations of the International Working Group, some cooperative group and most institutional phase II and pharmaceutical trials have adopted the WHO threshold for percentage marrow blasts as the criterion for the diagnosis of AML as well as their definitions of CR (complete remission) and other categories of response. At the present time, some of the large cooperative group trials retain the FAB criteria for purposes of comparability of 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 International Working Group revised diagnostic and response criteria for AML in 2001 to reflect current understanding of acute myeloid leukemia. Although roughly 75% of patients with acute leukemia can be categorized as myeloid or lymphoid lineage based on routine cytochemistries, immunophenotyping is necessary for proper diagnosis in a subset of patients, particularly those with undifferentiated morphology. In many large institutions, immunophenotyping is more rapidly available than cytochemistry, thus facilitating earlier initiation of therapy. 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 will require consultation with an experienced hematopathologist. Aberrant expression of differentiation antigens present at diagnosis may allow tracking of residual abnormal cells by flow cytometry in follow-up samples that may appear normal by conventional morphology. However, the role of immunophenotyping and molecular markers to monitor minimal residual disease in adult AML remains an area of research interest at present.

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 recent update, of 1,213 AML patients treated on CALGB protocols, the 5-year survival rate was 55% for patients with favorable cytogenetics, 24% for patients with intermediate risk, and 5% for those with poor risk cytogenetics.

Therefore the importance of obtaining sufficient samples on marrow or peripheral blood at diagnosis cannot be overemphasized. In addition to basic cytogenetic analysis, new molecular markers are helping to refine prognostics groups. These include FLT3, c-KIT and NPM1. At present tests for these molecular markers are not commonly available in the community; it is important to preserve additional aliquots of cryopreserved marrow from the time of diagnosis for possible future use. The two most common molecular markers are internal tandem duplication of the FLT3 gene encoding a
transmembrane growth factor receptor and mutations of the nucleophosmin gene (NPM1) which encodes a shuttling protein within the nucleolus. Both may be found either as isolated or double mutations commonly in patients with normal karyotypes. An isolated NPM1 mutation which localizes to the cytoplasm confers an improved survival to patients with normal karyotype similar to patients with favorable cytogenetics. Several recent large series have studied the impact of partial tandem duplication of mutations of FLT3 as an independent predictor of relapse free survival. In one report, patients with an isolated FLT3 mutation or tandem duplication had a 5 year survival of 20% vs. 42% for those without an abnormality. Patients who have combined NPM1 and FLT3 mutations have intermediate risk. 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 alters the risk of relapse. While none of these abnormalities affect the initial treatment, they provide information which 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.

Extramedullary presentation, including CNS disease are uncommon events in AML. Patients with significant CNS signs or symptoms at presentation should be evaluated radiographically for intracranial bleeding, leptomeningeal disease or mass lesions in either brain or spinal cord. If symptoms persist and bleeding and mass lesions are excluded, the patient should have a lumbar puncture (LP) for diagnostic and possible therapeutic purposes once coagulopathy has been corrected and adequate platelet support is available. Routine screening LP’s are not warranted in AML at diagnosis. However, patients with high risk of CNS disease such as those with monocytic differentiation (M4 or M5) or high WBC (>100,000/mcL) at diagnosis are recommended to have a diagnostic LP as part of the documentation of remission status.

For patients who present with solitary extramedullary disease (often referred to as granulocytic sarcoma or chloroma) without overt marrow disease, the initial treatment approach is systemic chemotherapy. Radiation or surgical resection may be incorporated at time of systemic chemotherapy in emergent situations, but these modalities, if needed at all, should optimally be deferred until count recovery to avoid excess toxicity.

Coagulopathy is fairly common at presentation in many leukemias; it is good clinical practice to screen for this problem with PT, PTT and fibrinogen as part of the initial work-up and before any invasive procedure. The need for a cardiac evaluation should be based on individual risk factors based on patient and family history or previous malignancy treated with cardiotoxic drugs or thoracic radiation. Human leukocyte antigen typing should be performed in all newly diagnosed AML patients for whom allogeneic hematopoietic cell transplantation (HCT) would be considered. HLA typing of family members should be considered for patients under age 55 who do not have favorable risk cytogenetics. Tissue typing should be broadened to include unrelated donors searches in patients under 55 with poor risk karyotypes or antecedent MDS/therapy related AML. Many institutions also use HLA typing to select platelet donors for allo-immunized patients.

At the completion of the initial work up, leukemias are broadly classified as acute promyelocytic leukemia (APL), acute myeloid leukemia (AML), or acute lymphoblastic leukemia (ALL). The following guidelines address only address the management of APL and AML in adults. ALL is not addressed in these guidelines.
Principles of Treatment

Treatment of acute leukemia has been divided into induction chemotherapy and post-remission (or consolidation) therapy. Although obtaining an initial remission is the first step in controlling the disease, it is also important that the patient emerge from the induction phase in condition to tolerate subsequent more intensive treatments during consolidation to achieve a durable remission. Patients who do not receive post-remission therapy will relapse, usually within 6 to 9 months. The induction strategy will be influenced by individual patient characteristics, such as age, presence of comorbid conditions affecting performance status, and pre-existing myelodysplasia. This is particularly true of elderly patients with AML. Patients with poor performance status who cannot tolerate chemotherapy should receive supportive care or a low-intensity clinical trial that would not produce the toxicities characteristic of current antineoplastic regimens. Strategies for consolidation therapy will be based on an assessment of the risk status of the leukemia, with higher risk patients receiving more aggressive therapy. At several points during the course of treatment, response is assessed, based on bone marrow morphology as well as cytogenetic and molecular responses. Finally, all patients require attentive supportive care related both to the underlying leukemia (i.e., tumor lysis syndrome) or the side effects of chemotherapy.

Acute Promyelocytic Leukemia (APL) Induction Therapy

The identification of fusion of the promyelocytic leukemia (PML) gene on chromosome 15 with the retinoic acid receptor (RAR) alpha gene on chromosome 17 is the molecular hallmark of APL. Additionally, earlier empiric observations on the efficacy of retinoic acid in inducing differentiation of APL cells led to treatment strategies which differ significantly from other subclasses of AML. In trials from Shanghai, complete response (CR) rates of 85% were reported with all-trans-retinoic acid (ATRA) as a single agent. The first US Intergroup trial that compared ATRA to conventional cytarabine and daunorubicin (7+3) confirmed similar CR rates of 70% for both treatments. The French APL91 trial comparing ATRA followed by cytarabine and daunorubicin versus combining ATRA with the chemotherapy showed comparable CR rates of 92% with either regimen but a lower relapse rate at 2 years for concomitant chemotherapy plus ATRA, with a 6% versus 16% relapse rate in those receiving sequential therapy. The Italian GIMEMA 93 trial and the Spanish PETHEMA LPA94 trial reduced the induction regimen to ATRA combined with idarubicin, yielding a 95% complete response (CR) rate, which has raised speculation as to the need for cytarabine. The trials differed in that in the PETHEMA trial consolidation consisted of 3 cycles of idarubicin alternating with mitoxantrone while the GIMEMA consolidation used these same agents, but paired them with either cytarabine and etoposide, VP-16; or cytarabine and 6-Thioguanine (6TG). Disease-free survivals were 86% and 90% respectively. In 2004 Sanz et al published a prognostic model for relapse-free survival using initial WBC < 10,000/mcL and platelets >40,000/mcL using data from this trial and a subsequent consolidation trial (LPA99). Low risk patients defined by WBC <10,000/mcL + platelets >40,000/mcL had (disease free survival) DFS of 97%; intermediate risk patients, defined by WBC <10,000/mcL + platelets <40,000/mcL, had a DFS of 82% and those with WBC >10,000/mcL had a DFS of 66%. In 2006, Ades et al reported the outcome of the French APL 2000 trial in which 340 patients under age 60 with WBC < 10,000 were randomized to receive cytarabine (Ara-C) or not during induction and consolidation along with daunorubicin and ATRA. Patients with WBC >10,000 or over age 60 all received cytarabine. While the complete remission rates were similar in the two groups, (99% with and 94% without Ara-C) those receiving cytarabine had a lower 2 year cumulative incidence of relapse that translated into an improved survival rate (93% at 2 years with Ara-C and 79% with no Ara-C). In patients with WBC > 10,000 the CR rate was 97% and the 2 year disease free survival was 89% for those under 60 years and 79%
for those over 60 years of age. For the majority of patients the role of cytarabine during induction remains controversial and therefore the panel recommends that initial therapy should consist of concomitant anthracycline based chemotherapy and ATRA (Category 1 recommendation). However for high risk patients the addition of cytarabine may offer some advantage.

To minimize early induction mortality due to coagulopathy, patients with a presumptive diagnosis of APL based on morphology, immunophenotype and DIC screen should promptly start ATRA and anthracycline without waiting for molecular confirmation. If the initial clinical diagnosis of APL is not confirmed by cytogenetic findings, ATRA will be discontinued and standard AML induction continued.

Recently, there has been interest in eliminating the anthracycline from induction regimens. Estey and colleagues studied an induction regimen combining ATRA and arsenic trioxide in 25 patients with low risk APL; 19 high risk patients were treated using the same regimen combined with gemtuzumab 9 mg/m^2 on day 1 of induction therapy. Complete remission was achieved in 24 of 25 patients with low risk disease and 15 of 19 patients with high risk disease. The authors suggest that ATRA plus arsenic trioxide may be an alternative to chemotherapy in patients with low risk APL. The NCCN guidelines indicate that ATRA plus arsenic trioxide is an alternative for patients who cannot tolerate anthracycline therapy. This induction regimen may be a particular consideration in the 19% of APL cases presenting in patients greater than 60 years old.

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”. It can occur with both ATRA and arsenic as single agents.

**Consolidation Therapy**

Because the differentiating action of ATRA occurs over a longer time period than the cyto reduction of conventional chemotherapy, early marrow evaluations are likely to be misleading and may lead to overtreatment. Therefore, a marrow evaluation is not recommended until there is recovery of blood counts. Cytogenetics have usually become normal by this point as well but molecular remission often requires at least two cycles of consolidation.

The goal of consolidation therapy for APL is the conversion of a morphologic and cytogenetic remission into a durable molecular remission. The data from the two sequential PETHEMA trials which produced the current risk model is being used to construct subsequent trials which intensify therapy for the high risk groups. In the second PETHEMA trial (LPA99) 15 days of ATRA were added to each of three cycles of anthracycline consolidation. For the low risk group there was no difference in relapse rate (3-6%) or in 3 year DFS (93-97%) with the ATRA group compared to a similar consolidation without ATRA in trial LPA94. For intermediate risk group the relapse rate was 2.5% vs. 14% in the historic control with a 3 year DFS of 97% vs. 82%. Although the addition of ATRA to the high risk group did improve relapse and DFS, there is room for improvement with a relapse rate of 21% and a 3 year DFS of 77%. In the French APL 2000 which randomized cytarabine usage in a daunorubicin consolidation, the low and intermediate groups had a 2 year DFS of 93% with cytarabine vs. 77% for the group without it. Thus the outcomes for consolidation with anthracycline plus ATRA or plus cytarabine are comparable for patient with intermediate risk APL. For high risk patients under age 60 the addition of cytarabine does appear to offer some benefit with a 2 year DFS of 89%. The US Intergroup trial which introduced the addition of 2 cycles of arsenic trioxide (ATO) to the prior backbone of cytarabine/daunorubicin consolidation did show improved relapse free survival in the ATO arm. However the outcomes do not appear to be superior to the less
complex consolidation schedules in the two European trials. Based on this data, the guidelines now recommend the use of ATRA in consolidation for patients with intermediate or high risk (Category 1 recommendation). For patients who received ATRA and ATO, the consolidation regimen consisted of ATRA for one week each month for seven months post remission and ATO intravenously for 5 consecutive days a week for three weeks on months 1, 3, 5 and 7. At 18 months 24/25 low/intermediate risk patients remain in molecular remission compared with 12/19 high risk patients.

Post-Consolidation Therapy

Following the consolidation therapy, patients are assessed for molecular remission using PCR techniques on bone marrow samples. For those that are PCR negative a 1-2 year course of ATRA maintenance therapy is recommended (Category 1 recommendation), which may be combined with 6-mercaptopurine and methotrexate. The recommendations for maintenance ATRA are derived from several trials which showed superior relapse-free survivals for patients receiving ATRA as maintenance. The French APL91 trial showed decreased relapse rates at 2 years for ATRA (21%), 6-mercaptopurine (6MP) + methotrexate (13%), and ATRA, 6MP + methotrexate (8%), versus no maintenance (35%). The US Intergroup trial showed superiority of disease-free survival for patients receiving maintenance ATRA versus no maintenance. All the recent trials cited above have used the triple maintenance regimen listed above. A maintenance regimen of ATRA 1 week on and 1 week off is currently under investigation. The need for maintenance in low risk patients who achieve molecular remission post consolidation is also an area under investigation.

Patients should be monitored with RT-PCR on bone marrow samples for PML/RARα fusion transcript at the end of consolidation and at a minimum of every 3 months for 2 years and then every 6 months (as a minimum) for 2-3 years. At the current level of resolution, a change from PCR negative to positive should be confirmed by peripheral blood or bone marrow in a reliable laboratory 4 weeks later. If molecular relapse is confirmed by a second positive test, intervention should be strongly considered. If the second test was negative frequent monitoring every 3 months for 2 years is strongly suggested to confirm that the patients remain negative.

Postremission Therapy

Patients who are not in molecular remission at completion of consolidation or who become PCR positive are initially treated with arsenic trioxide. Molecular remissions have been achieved in 80% of patients treated for either clinical or molecular relapse in several studies from China, US, and Europe. Patients who achieve a molecular remission with arsenic trioxide as second line therapy should be considered for autologous HSCT, if they do not have contraindications to high dose therapy. Patients who received a PCR-negative autograft had a 75% 7-year overall survival in a recent retrospective study published by the European APL Group, compared to a 52% overall survival for patients receiving allogeneic HSCT. The differences in survival are accounted for by high treatment-related mortality in the allogeneic group, which influences the guideline recommendations to reserve allogeneic transplant for those who have persistent disease despite salvage therapy. For patients in second CR who have contraindications to HSCT, maintenance therapy with arsenic trioxide is an option in the absence of an appropriate clinical trial. For patients with persistent disease following arsenic trioxide who are not allogeneic transplant candidates, options include a clinical trial or gemtuzumab ozogamicin. Gemtuzumab ozogamicin has shown significant activity in relapsed APL.
Acute Myeloid Leukemia

Most initial treatment decisions for AML are based on age, history of prior myelodysplasia or cytotoxic therapy and performance status. Although cytogenetics is the most powerful predictor of disease-free survival, in most instances induction chemotherapy 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 to restore normal hematopoiesis.

Recommendations for induction chemotherapy for patients with AML consider age 60 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 over 60 years of age, as well as 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, there is substantial opportunity for innovative clinical trials for both patient populations. These guidelines consider patients older or younger than 60 years old separately.

Patients Younger than 60

Induction Therapy

Standard induction regimens are appropriate for patients younger than age 60 who have no antecedent hematologic disease, such as myelodysplastic syndrome or treatment related secondary AML. These regimens are based on a backbone of cytarabine and an anthracycline (or anthracenedione) and have changed little in the last 25 years. Historically, in most large cooperative group trials, daunorubicin has been the most common anthracycline. However, idarubicin, which has a longer intracellular retention time, has also been used. The merits of dose-intensive cytarabine therapy during induction have been explored in two large cooperative clinical trials. In an Australian Leukemia Study Group trial, 301 patients under age 60 years were randomized to receive either high dose cytarabine (3 g/m² q12h on days 1, 3, 5, and 7 for a total of 24 g/m²) or standard cytarabine therapy (100 mg/m²/d x 7 days via continuous infusion); both arms received daunorubicin (50 mg/m² on days 1 to 3) and etoposide (75 mg/m²/d x 7 days). The CR rates were equivalent in both arms (71% and 74%, respectively), although treatment-related morbidity and mortality were higher in the high dose arm. However, with patients in both arms of the study received only two cycles of standard dose cytarabine, 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.

In a Southwestern Oncology Group (SWOG) study, 22 patients were randomized to receive high dose cytarabine (2 g/m² every 12 hours x 6 days for a total of 24 g/m²) or standard-dose cytarabine (200 mg/m²/d x 7 days); patients in both treatment arms also received daunorubicin (45 mg/m²/d x 3 days). Patients receiving high dose cytarabine induction therapy received a second high dose cycle for consolidation, and patients in the standard-dose treatment arm were randomized to receive either two cycles of standard dose cytarabine consolidation or one cycle of high dose cytarabine plus daunorubicin consolidation. The complete response rates were again equivalent: 55% for the high dose cytarabine treatment arm compared with 58% for the standard-dose arm for patients under 50 years; and 45% for high dose cytarabine versus 53% for standard-dose therapy for patients 50 to 65 years of age. Patients in the high dose cytarabine arm experienced higher treatment-related mortality (12% vs. 5%) and neurologic toxicity.

Younger patients who received both high dose cytarabine induction and consolidation in the SWOG trial had the best survival (52%) and
disease-free survival (34%) rates at 4 years, when compared with standard induction and consolidation (34% survival and 24% disease-free survival) or standard induction with high dose consolidation (23% survival and 14% disease-free survival). However, the percentage of patients achieving a CR who did not proceed to consolidation was twice as high in the high dose cytarabine induction arm. The use of high dose cytarabine induction outside a clinical trial remains controversial. The risks for neurotoxicity and renal insufficiency are increased with high dose cytarabine and both renal and neurologic function should be closely monitored in patients receiving such treatment.

In a Cancer and Leukemia Group B (CALGB) trial, patients who received standard-dose cytarabine-daunorubicin induction therapy and three to four courses of high dose cytarabine consolidation also achieved a 4-year disease-free interval of 44% with similar rates of neurotoxicity and treatment-related mortality. Because the remission rates are comparable, the decision to use high dose cytarabine versus standard-dose cytarabine for induction will be influenced by consolidation strategies; fewer high dose consolidation cycles may be needed for patients induced with high dose cytarabine or for patients who will undergo early autologous stem cell transplantation, versus standard-dose induction and 3 to 4 cycles of high dose cytarabine consolidation. High dose cytarabine induction therapy is considered a category 2B recommendation.

With either high- or standard-dose cytarabine-based induction for younger patients, between 20% and 45% of these patients will not enter remission. In a recent report of 122 patients treated with high dose cytarabine 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.

Patients with antecedent hematologic disease or treatment related secondary leukemia are considered poor risk patients, unless they have favorable cytogenetics such as t(8;21) or inv(16). In addition, patients with unfavorable karyotypes such as -7, -5, 11q23 abnormalities or complex cytogenetic abnormalities are also considered poor risk and are treated similarly. This group of patients should be entered into a clinical trial (incorporating either chemotherapy or low-intensity therapy), if available, since only 40% to 50% of these patients achieve CR with standard induction therapy, and response durations are short. In addition, HLA testing should be done promptly in those who may be candidates for either a fully ablative or a reduced intensity allogeneic HSCT as a transplant from a sibling or an unrelated donor constitutes the best option for long-term disease control. Due to the decreased probability of achieving remission through induction chemotherapy, transplantation without induction chemotherapy may be considered for patients with antecedent myelodysplasia or treatment-related leukemia who have an available sibling donor. In an EBMT trial, patients with high risk myelodysplasia or AML evolving from myelodysplasia who received allogeneic transplantation without prior chemotherapy had a 25% 3-year disease-free survival. Patients who received antecedent chemotherapy and achieved a CR had a 45% disease-free survival, compared with 10% for patients who did not respond to chemotherapy before transplantation.

**Post Induction Therapy**

To evaluate the efficacy of the induction regimen, the panel recommends repeating a bone marrow test 7 to 10 days after completion of induction. In patients who have received standard-dose cytarabine induction and still have significant residual blasts, or significant cytoreduction without hypoplasia, additional therapy with standard-dose cytarabine and anthracycline (or anthracyclinedione) should be considered. Additional options for those with significant residual blasts or those with induction failure include high dose
cytarabine with or without an anthracycline, an allo-HSCT with a matched sibling or alternative donor, participation in a clinical trial or best supportive care. If the marrow is hypoplastic (defined as cellularity <10-20% and residual blasts <5-10%), treatment selection must be deferred until there is marrow recovery and the remission status can be assessed.

Patients initially treated with high dose cytarabine and who have significant residual blasts 7-10 days after completion of chemotherapy are considered to have induction failure. Additional high dose cytarabine is unlikely to induce remission. If a sibling 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, patients with both myeloid and lymphoid markers at diagnosis (biphenotypic leukemia) may respond to acute lymphoblastic leukemia (ALL) therapy if they failed an AML induction regimen. 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.

Post-remission Therapy
Since 1994, multiple (3-4) cycles of high dose cytarabine therapy have been the non-protocol standard consolidation regimen for patients under 60 years of age 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 (irrespective of cytogenetic risk group) 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 break down disease-free survival rates by cytogenetic subgroups, subsequent analysis showed a disease-free survival rate of 60% for patients with good-risk cytogenetics, 30% for intermediate-risk cytogenetics, and 12% for poor-risk cytogenetics in patients receiving high dose cytarabine consolidation; these outcomes are similar to those on the high dose treatment arm in the SWOG trial.

Choices for consolidation strategies currently are: 1) multiple cycles of high dose cytarabine, 2) one or more cycles of high dose cytarabine followed by autologous HCT or 3) allogeneic stem cell transplantation from sibling or unrelated donors. The decisions regarding autologous and allogeneic HSCT are strongly influenced by the (1) expected relapse rate with standard 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. A recent comparison of autologous versus allogeneic HSCT was a combined EORTC/GIMEMA trial for patients less than age 46 with results stratified by cytogenetic risks: good [t(8;21) or inv(16)]; normal, and poor (all other abnormalities). In the good risk group disease-free survival was 66% for autologous HSCT and 62% for allogeneic HSCT, with 6% treatment related mortality (TRM) for autologous HSCT and 17% for allogeneic HSCT. The autologous results are comparable to the CALGB data on multiple cycles of high dose cytarabine both for relapse-free survival and mortality.

The NCCN AML panel members did not reach a consensus on a single preferred post-remission strategy for patients with better-risk cytogenetics. Either multiple cycles of dose-intensive consolidation (Category 1) or one cycle of dose-intensive (high dose cytarabine) consolidation followed by autologous transplantation (category 2B) can produce good survival rates (60-65%) in this group. 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 who require two cycles of chemotherapy to achieve a remission are at very high risk for relapse and should be considered for either clinical trial or allogeneic transplant as initial consolidation whenever possible. Emerging data suggest that patients with t(8;21) who also have a c-KIT mutation have a higher risk of relapse and may be a candidate for clinical trial. The long-term toxicities of allogeneic HSCT are considered prohibitive for patients with good risk cytogenetics; the panel would reserve this option for patients who experience relapse.

Panel members achieved more consensus that transplant-based options using either sibling or autologous stem cell sources were an appropriate strategy for patients with intermediate-risk cytogenetics. In the EORTC/GIMEMA trial, the 4-year DFS was 48.5% for allogeneic and 45% for autologous HCT in patients with normal cytogenetics. Other options for this group include clinical trials or high dose cytarabine consolidation. Alternative regimens incorporating intermediate doses of cytarabine are also acceptable in this group. Comparable 5-year DFS were reported this year in AML patients <60 years with normal karyotype after either four cycles of intermediate or high dose cytarabine (41%) or autologous HSCT (45%).27 A clinical trial is another appropriate option. A large German trial has revealed additional molecular prognostic markers for patients with “normal” karyotype. The presence of an isolated mutant NMP1 cytoplasmic shuttle protein improves prognosis to that comparable to patients with better risk cytogenetics. If this situation it would be a reasonable option to delay transplantation until relapse. In contrast, patients with an isolated FLT3 mutation and normal karyotype have an outlook similar to those with poor risk cytogenetics and should be considered for a clinical trial or early allogeneic transplantation.

The panel uniformly endorsed allogeneic HSCT with sibling or unrelated donors or clinical trial as consolidation therapy for patients with poor-risk cytogenetics or patients with therapy-related AML or prior myelodysplasia. Sibling allogeneic HSCT produced a 43% DFS rate in this group of patients in the EORTC/GIMEMA trial, with similar outcomes for unrelated donor recipients reported by the International Bone Marrow Transplant Registry (IBMTR). The outcome for autologous HSCT was comparable to chemotherapy, with 18% DFS. The NCCN AML panel members strongly recommend clinical trials as standard therapy for patients with poor prognostic features, which also include high WBC, CD56+, FLT3 abnormalities in the setting of otherwise normal karyotype or two cycles needed to achieve CR.

Patients 60 and Older

Induction Therapy

The creation of separate algorithms for patients older than 60 recognizes the poor outcomes in this group with standard therapy. Additionally, standard dose induction therapy is not appropriate for patients aged 75 or older, those with significant comorbidities that cause organ dysfunctions not related to leukemia, or patients between 60 and 75 years old with a performance status greater than 2.28, 29 In addition to a clinical trial, options include low intensity therapy or best supportive care.

Patients between the ages of 60 and 75 with a performance status of 2 or less are initially evaluated with cytogenetics to determine if the leukemia is associated with more than three karyotypic abnormalities, referred to as complex cytogenetics. Patients with complex cytogenetics have a poor prognosis and thus are not candidates for standard induction therapy. Therefore, it is very helpful to obtain cytogenetic analysis before initiating therapy, if possible. A clinical trial for patients with non-complex cytogenetics is preferred, but standard dose cytarabine with an anthracycline or anthracyclinedione is another option.
Post-Induction Therapy

Similar to younger patients, elderly patients are evaluated with a bone marrow 7-10 days after completion of chemotherapy and categorized according to the presence of blasts or hypoplasia. Patients with significant cyto reduction without hypoplasia may receive standard-dose cytarabine with an anthracycline or anthracyclene. A repeat bone marrow is performed in these patients and in those with hypoplasia following induction to document the remission status. Those achieving a complete remission may receive further cytarabine with or without an anthracycline. Patients with a good performance status, normal renal function and a normal or low risk karyotype may additionally consider higher doses of cytarabine (1-1.5 g/m²/d x 4-6 doses) without an anthracycline.

The role of myeloablative allo-HSCT is limited in older patients due to significant morbidities, but there has been ongoing interest in reduced intensity allogeneic HSCT as consolidation therapy. Case series and analyses of registries have reported encouraging results regarding overall survival and nonrelapse mortality. Estey and colleagues prospectively evaluated a protocol where patients over the age of 50 with unfavorable cytogenetics would be evaluated for a reduced intensity allo-HSCT. Of the 259 initial patients, only 14 ultimately underwent transplantation, due to illness, lack of donor, refusal or unspecified reasons. The authors compared the results with matched cases receiving conventional dose chemotherapy. This analysis suggested that the reduced intensity allo-HSCT was associated with improved remission survival and the authors concluded that this approach remains of interest. However, the small number of patients who ultimately qualify for this therapy remains a significant limitation.

The guidelines note that when offered in the context of a clinical trial, reduced intensity allo-HSCT is considered an additional option for patients 60 years and older for the following indications:

- As a post-remission therapy for those achieving a complete response to induction therapy
- For treatment of induction failure.

Post-Remission Surveillance and Salvage Therapy

Complete blood counts including platelets should be monitored every 1-3 months for the first 2 years after patients have completed consolidation, then every 3-6 months for a total of 5 years. Bone marrow evaluation is recommended only if the hemogram becomes abnormal, rather than as part of routine surveillance of the bone marrow at fixed intervals, unless this is being done as part of a research protocol. Finally, a matched unrelated donor search may be initiated for high risk patients in CR1 or considered at first relapse in appropriate patients concomitant with initiation of therapy.

Treatment strategies for relapse are categorized according to the patient’s age. For patients younger than 60 years who have experienced an early (<6 months) relapse after induction chemotherapy, Phase I or II trials are considered an appropriate strategy. If the relapse is detected when the tumor burden is low and the patient has a previously identified sibling or unrelated donor, allogeneic HSCT can be considered as primary therapy following salvage chemotherapy.

In patients younger than 60 who have relapsed after a “long” (>6 months) remission, re-induction therapy using either the initial regimen or new agents in the setting of a clinical trial is appropriate. After achieving a second remission, these patients would also be candidates for transplantation using either an allogeneic graft of family or registry origin or autologous stem cells if no donor is available.

Patients 60 years or older with relapse beyond 6 months who are robust and wish to continue treatment after relapse may be offered salvage therapy with: 1) clinical trial (strongly preferred), 2)
gemtuzumab or 3) repetition of the initial induction therapy, if they had a long initial remission. Best supportive care is always an option for those who do not wish to pursue intensive treatment.

Gemtuzumab ozogamicin calicheamicin conjugated with an anti-CD33 monoclonal antibody was approved for the treatment of relapsed AML in older patients. Gemtuzumab as a single agent produced clearance of marrow and peripheral blood blasts and transfusion independence in 26% of patients over age 60 with blasts expressing CD33. Therapy-related toxicity was low, with infusional side effects of fever, chills and hypotension as the main acute reactions. Some patients continued to have persistently low platelet counts without evidence of persistent leukemia. Liver function abnormalities were seen in 24% of patients, particularly when this agent was combined with hepatotoxic agents. Exposure to gemtuzumab within 3-4 months of HSCT has been reported to increase the risk of veno-occlusive disease-like syndrome. In this setting the dose should be reduced by 30-50%.

Evaluation and Treatment of CNS Leukemia

Leptomeningeal involvement is much less frequent in AML compared to ALL; therefore, the NCCN panel does not recommend lumbar punctures as part the routine diagnostic work up. However, if there are neurologic symptoms 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 there is no mass effect, the patient can undergo a lumbar puncture (LP). If the LP is negative, the patient can be observed with a repeat LP if symptoms persist. If the LP is positive, intrathecal chemotherapy with cytarabine or methotrexate is recommended concurrent with systemic induction therapy. Initially the intrathecal therapy is given twice a week until the LP is normal, and then weekly for 4-6 weeks. High dose cytarabine induction therapy may substitute for intrathecal chemotherapy since it crosses the blood-brain barrier; the CSF must then be reassessed after induction and further therapy given as appropriate. One should, however, bear in mind that high dose cytarabine and cranial radiation used concomitantly may carry increased risks of neurotoxicity.

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 strongly be considered followed by intrathecal therapy, as described above.

The panel does not recommend routine screening for occult CNS disease in the majority of patients with AML in remission. The exceptions are patients with M4 or M5 morphology, or WBC >100,000/mcL at diagnosis. For patients with positive cytology, the panel recommended either intrathecal chemotherapy, as outlined previously, or documenting clearance of CNS disease after the first cycle of high dose cytarabine chemotherapy. In addition to the recommended evaluation and treatment of CNS leukemia, further CNS surveillance is recommended based upon institutional policy and practice.

Monitoring and Supportive Care

Growth-factor support may be considered for older patients after chemotherapy is complete. This recommendation is based on an Eastern Cooperative Oncology Group (ECOG) study. Recommendations on the use of cytokines for infection or for slow marrow recovery are left to institutional policy. G-CSF should have been discontinued for a minimum 7 days before obtaining a bone marrow to document response because of effects on marrow morphology.

Leukocyte-depleted products should be used for transfusion. 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 time of diagnosis. Radiation of all blood products is
advised to reduce the risk of graft-versus-host disease in all immunosuppressed patients.

The standard tumor lysis prophylaxis is hydration with alkalinization of the urine and allopurinol administration. Rasburicase (genetically engineered recombinant form of urate oxidase enzyme) therapy should be considered if the patient is unable to tolerate oral medication, has clinical evidence of tumor lysis syndrome, or problematic hyperuricemia.

Patients who receive high dose cytarabine need to be closely monitored for changes in renal function. Renal dysfunction is highly correlated with increased risk of cerebellar toxicity. Patients need to be monitored for nystagmus, dysmetria, and ataxia before each dose of high dose cytarabine; patients exhibiting any neurologic signs should discontinue high dose cytarabine, and all subsequent cytarabine therapy must be standard-dose, rather than high dose. In patients who develop cerebellar toxicity, the patient should not be re-challenged with high dose cytarabine in future treatment cycles. High dose cytarabine should also be discontinued in patients with rapidly rising creatinine caused by tumor lysis.

Specific supportive care issues should be considered when treating patients with APL. The first is the development of the “retinoic acid syndrome” of which the initial signs and symptoms are fever, often an increasing WBC over 10,000/mcL at initial diagnosis or at relapse, and fluid retention. Patients with these findings should be closely monitored for hypoxia, the development of pulmonary infiltrates or pleural effusion. If any of these findings occur, patients should be started on dexamethasone 10 mg twice a day for 3 to 5 days, the dose is then tapered over two weeks. ATRA may need to be held during the initial acute symptomatic period but may be restarted when symptoms improve. Arsenic trioxide may induce a similar syndrome called the “APL differentiation syndrome” which also responds to dexamethasone.

Arsenic trioxide therapy may prolong the QT interval, making patients susceptible to ventricular arrhythmias. Therefore, prior to therapy an EKG is recommended to assess prolonged QT interval. Serum electrolytes should also be evaluated prior to therapy. During therapy careful monitoring to maintain electrolytes (Ca ≥9.0, K ≥4.0, Mg ≥1.8) in the upper normal range and avoidance of other drugs that prolong the QT interval will lessen the risk of cardiac arrhythmias. Patients with an absolute QT interval greater than 500 m/sec should be reassessed.

Leukapheresis is not recommended in the routine management of patients with high white blood cell counts in APL 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.

Disclosures for the NCCN AML Guidelines Panel
At the beginning of each panel meeting to develop NCCN guidelines, panel members disclosed financial support they have received in the form of research support, advisory committee membership, or speakers' bureau participation. Members of the panel indicated that they have received support from the following: Berlex, Inc., Celgene, Cell Genesys, Inc., Cell Therapeutics, Inc., Genentech, Genzyme, Millennium, Novartis, Ortho Biotech, and Tibotec.

Some panel members do not accept any support from industry. The panel did not regard any potential conflicts of interest as sufficient reason to disallow participation in panel deliberations by any member.
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