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Featured Updates to the NCCN Guidelines

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Abstract

These NCCN Guidelines Insights summarize several key updates to the NCCN Guidelines for Acute Myeloid Leukemia and discuss the clinical evidence that support the recommendations. The

updates described in this article focus on the acute promyelocytic leukemia (APL) section, featuring recommendations for additional induction/consolidation regimens in patients with low- or intermediate-risk APL, and providing guidance on maintenance strategies for APL.

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Learning Objectives

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

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

Overview

Acute myeloid leukemia (AML) represents a heterogeneous hematologic malignancy characterized by the clonal expansion of myeloid blasts in the peripheral blood and bone marrow. AML remains the most common form of acute leukemia diagnosed in adults,

accounting for the largest number of annual deaths from leukemias in the United States. Approximately 14,590 new cases of AML and 10,370 deaths from the malignancy are estimated in 2013.[1] The age-adjusted annual incidence rate of AML is 3.7 per 100,000 persons.[2] Historically, acute promy-elocytic leukemia (APL), which constitutes approximately 10% of AML cases, has been a particularly life-threatening subtype of AML, with a distinct morphology and clinical presentation.[3–5] In a recent analysis of a data set from the SEER registry (1992– 2007), the age-adjusted annual incidence of APL was 0.23 per 100,000 persons.[6] The median age at APL diagnosis was 44 years, which is younger than that of patients with AML (median age, 67 years).[2,6] Cytogenetically, APL is distinguished by the presence of the translocation t(15;17)(q24.1;q21.1), which involves fusion of the promyelocytic leukemia gene (*PML*) on chromosome 15 to the retinoic acid receptor alpha gene (*RARA*) on chromosome 17, resulting in the characteristic *PML-RARA* fusion gene.[3,4] Although APL is highly curable in a large proportion of patients, it can be associated with severe coagulopathy, which remains the primary cause of early death from hemorrhagic events (especially during induction therapy).

Induction/Consolidation Regimen for Low- and Intermediate-Risk APL

The incorporation of all-trans retinoic acid (ATRA) and the use of risk stratification approaches have dramatically improved outcomes for patients with APL. Induction regimens with ATRA combined with anthracyclines, with or without cytarabine, show complete remission (CR) rates exceeding 90% in several large cooperative group trials.[7–10] Using ATRA-based induction regimens followed by consolidation with regimens containing ATRA with anthracyclines, or cytarabine with anthracyclines, more than 80% of patients with APL can be cured.[7,9–11]

Risk stratification is a major consideration in the treatment of APL (see AML-2, page 1049).[10] Patients with low- or intermediate-risk disease (WBC count ≤10,000/mcL) are typically treated with less-intensive consolidation regimens compared with those used to treat high-risk patients (WBC count >10,000/mcL), depending on the treatment protocol used. In the APL 2000 study (which included dauno-rubicin and cytarabine, but no ATRA, for consolidation), “standard-risk” (low- or intermediate-risk) patients received a lower dose of cytarabine during consolidation than the high-risk patients,[8,12] and in the LPA 2005 and AIDA 2000 protocols (which included ATRA, mitoxantrone, and idarubicin, with or without cytarabine, for consolidation), cytarabine was omitted during consolidation in low-or intermediate-risk patients.[10,11] With the consolidation regimens evaluated in the LPA 2005 study, outcomes were similar between low- and intermediate-risk groups regarding the 3-year cumulative incidence of relapse (6% for both), disease-free survival (DFS; 93% vs 94%) and overall survival (OS; 96% vs 93%).[10] In the GIMEMA AIDA 2000 study, low- and intermediate-risk patients were treated as a single category, and received the same consolidation regimen with ATRA, mitoxantrone, and idarubicin; in this group, the 6-year cumulative incidence of relapse was 11%, and the 6-year DFS and OS rates were 86% and 89%, respectively.[11]

Another agent that has contributed to the evolution in APL therapy is arsenic trioxide (ATO). ATO promotes apoptosis of APL cells, and has been shown to act synergistically

with ATRA.[13,14] The addition of ATO as first-line consolidation therapy with ATRA and anthracycline (following standard induction with ATRA, anthracycline, and cytarabine) resulted in improved outcomes in the North American Intergroup trial.[9] Induction regimens with ATO combined with ATRA (without chemotherapy) induced CR rates exceeding 90%, and recent studies have shown the efficacy of using ATO and ATRA during induction and consolidation (while omitting the use of chemotherapy) in patients with low- or intermediate-risk APL or those who cannot tolerate regimens containing anthracyclines.[15–17]

In patients with low- or intermediate-risk APL, ATRA combined with ATO is a new addition to the standard of care based on results from a recent randomized trial that compared this regimen with the standard AIDA (ATRA plus idarubicin) regimen.[16] In a phase III randomized trial of the Italian-German Cooperative Group, induction with ATRA combined with ATO was compared with the AIDA regimen in patients with newly diagnosed low- or intermediate-risk APL (N=162; APL-0406 study).[16] Patients in Arm A received ATRA (45 mg/m^2) plus ATO (0.15 mg/kg) daily until CR, then AT O 5 days per week for 4 weeks every 8 weeks for a total of 4 courses, and ATRA daily for 2 weeks every 4 weeks for a total of 7 courses. Patients in Arm B received the standard AIDA induction followed by 3 cycles of anthracycline-based consolidation combined with ATRA and then maintenance comprising low-dose chemotherapy and ATRA.[11]

The primary end point of this study was the 2-year event-free survival (EFS) rate. Among evaluable patients (n=156), CR rates after induction were not different between Arms A and B (100% vs 95%). Four deaths occurred in Arm B during induction therapy (2 of which were caused by differentiation syndrome). One death in Arm A and 3 in Arm B occurred during consolidation. Grade 3 or 4 neutrope-nia and thrombocytopenia lasting more than 15 days were significantly more frequent in Arm B compared with Arm A throughout the induction and consolidation cycles. Grade 3 or 4 hepatic toxicities occurred significantly more frequently in Arm A (63% vs 6%; $P<.001$).[16] After a median follow-up of 34.4 months, the 2-year EFS rate was significantly higher in Arm A (97% vs 86%; $P<.001$ for noninferiority; $P=.02$ for superiority). The 2-year OS probability was also significantly higher in Arm A (99% vs 91%; $P=.02$). The 2-year cumulative incidence of relapse was not significantly different between the treatment arms (1% and 6%, respectively).[16] This randomized study showed noninferiority of an ATRA- plus-ATO regimen compared with AIDA, which may allow for elimination of chemotherapy agents in the initial treatment of patients with non–high-risk APL.

NCCN Recommendations

For low- or intermediate-risk patients (WBC counts ≤10,000/mcL), the NCCN AML Panel recommends initial induction with either ATRA plus ATO[16]; ATRA plus idarubicin alone (AIDA regimen)[10] (category 1); ATRA plus daunorubicin and cytarabine[8,9,18] (category 1 for the French APL 2000 protocol[8]); or enrollment in a clinical trial (see AML-4, page 1050). The panel has positioned the ATRA-plus-ATO regimen first, based on results from the APL-0406 phase III randomized trial.[16] The panel also recommends the ATRA-plus-

ATO regimen for patients with high-risk disease who cannot tolerate anthracycline-containing therapy (see AML-2, page 1049).

The AIDA 2000 regimen may be positioned slightly higher than either the French APL 2000 or the North American Intergroup regimens because of the ease of administration and potentially decreased toxicity. However, all 4 of these regimens yield excellent results. Treatment protocols must be followed consistently throughout all components of the treatment phase, from induction to consolidation; induction regimens from one trial should not be used with consolidation regimens from another trial. Given data from recent studies that suggest similar outcomes for patients with low- or intermediate-risk disease, these patients are considered as a single category and treated with the same induction and consolidation regimens (see AML-4, page 1050).

Approaches to Maintenance Therapy in APL

The *PML-RARA* fusion gene can be quantitatively monitored using PCR assays to document disease burden and confirm postconsolidation molecular remission status in patients with APL. Considerable debate remains regarding the use and frequency of molecular monitoring and incorporation of maintenance therapy in the management of APL. Earlier studies have suggested the benefit of postconsolidation maintenance with ATRA (with or without chemotherapy) in terms of improved remission durations.[7,18]

The French APL93 trial randomized eligible patients (n=289) to 4 differentmaintenance regimens: no maintenance, intermittent ATRA, continuous chemotherapy (with 6-mercaptopurine and methotrexate), and the combination of ATRA with chemotherapy.[19] Results showed decreased 2-year relapse rates with continuous chemotherapy (11.5% vs 27% with no chemotherapy) and ATRA (13.5% vs 25% with no ATRA). Results of long-term follow-up from this trial showed a beneficial effect of maintenance with intermittent ATRA and continuous chemotherapy, with an additive effect of the 2 modalities; the 10-year cumulative relapse rates with no maintenance, ATRA alone, continuous chemotherapy, and ATRA combined with chemotherapy were 43%, 33%, 23%, and 13%, respectively ($P<.001$).[7] Patients at high risk (defined in this study as WBC count >5000/mcL) derived the most benefit from maintenance; the 10-year cumulative relapse rates among high-risk patients who received no maintenance, ATRA alone, continuous chemotherapy, and ATRA combined with chemotherapy were 68%, 53%, 33%, and 21%, respectively ($P<.001$). No statistically significant difference in 10-year relapse rates was observed among patients with lower-risk disease, although the relapse rate dropped from 29% without maintenance to 11.5% with ATRA combined with chemotherapy. The 10-year OS rates with no maintenance, ATRA alone, continuous chemotherapy, and ATRA combined with chemotherapy, were 74%, 88%, 93%, and 94%, respectively ($P<.001$).[7]

The first North American Intergroup trial showed superior DFS outcomes for patients receiving maintenance ATRA compared with no main-tenance.[18] In this trial, patients were randomized to induction with chemotherapy (daunorubicin and cytarabine) or ATRA, and subsequently underwent a second randomization to either maintenance with ATRA or no maintenance (observation only). Consolidation therapy comprised the initial induction

therapy regimen for course 1, and then daunorubicin and high-dose cytarabine for course 2. In this trial, molecular remission status was not assessed before randomization to maintenance. The 5-year DFS rates for the 4 randomization groups—chemotherapy induction plus observation, chemotherapy induction plus ATRA maintenance, ATRA induction plus observation, and ATRA induction plus ATRA maintenance—were 16%, 47%, 55%, and 74%, respectively.[18] Although the incorporation of ATRA during induction and maintenance seemed to improve long-term remission durations, the role of maintenance therapy is less clear, because treatment strategies have evolved to incorporate ATRA or ATO into consolidation regimens. This is particularly a point of debate for low-risk patients who experience a molecular remission at the end of consolidation.

Data from other recent studies have not shown any long-term benefit with the use of maintenance therapy in patients who achieve molecular remission after consolidation.[20,21] The Japanese APL97 randomized study evaluated the role of maintenance with in-tensifed chemotherapy versus observation in patients in molecular remission after consolidation (n=175).[20] The estimated 6-year DFS rate was not significantly different between the chemotherapy maintenance and observation arms (63% vs 80%). The estimated 6-year OS rate was significantly lower with chemotherapy maintenance (86% vs 99%; *P*=.014), which the investigators attributed to the potential effects of chemotherapy maintenance on the development of secondary malignancies and on responses to subsequent (second-line) therapies.[20]

The AIDA 0493 trial initially randomized patients who were in postconsolidation molecular remission to 4 maintenance approaches (n=318): chemotherapy (with 6-mercaptopurine and metho-trexate), ATRA alone, ATRA in combination with chemotherapy, or observation only.[21,22] The study protocol was later amended to include only the 2 ATRA-containing maintenance arms (additional patients, n=268). ATRA was not given during consolidation. Among all patients experiencing molecular remission who were randomized to maintenance (n=586), the estimated 12-year molecular DFS rate was 71%.[21] Among those randomized to the initial 4 maintenance arms, no significant differences in outcomes were observed between maintenance approaches; the estimated 12-year molecular DFS rates were 70% with chemotherapy, 69% with ATRA alone, 68% with ATRA combined with chemotherapy, and 69% with observation only. Among the patients who were enrolled and randomized to ATRA-containing maintenance arms following the protocol amendment, the estimated 10-year molecular DFS rates were 73% with ATRA alone and 74% with ATRA combined with chemotherapy. These studies showed that maintenance therapy provided no longterm benefit in patients with APL who experienced molecular remission after consolidation. With contemporary treatment strategies that incorporate ATRA and/or ATO into consolidation regimens, the role of maintenance becomes even less clear. The benefit of maintenance therapy likely depends on the regimens used during induction and consolidation therapies. Therefore, maintenance therapy must be used in conjunction with the treatment protocols in which it has been shown to confer benefit.

Further data from randomized trials are needed to address the question of maintenance. A phase III cooperative group trial (SWOG 0521) has been designed to examine the need for maintenance therapy (using the combination of ATRA, 6-mercaptopu-rine, and

methotrexate) in patients with low- or intermediate-risk APL. In this ongoing trial, patients receive induction therapy with ATRA, daunorubicin, and cytarabine, followed by consolidation therapy with ATO, ATRA, and daunorubicin. Patients are then randomized to receive maintenance therapy or no further treatment (observation only).

NCCN Recommendations

The NCCN AML Panel recommends that PCR be performed on a bone marrow sample at the completion of consolidation to document molecular remission (see AML-5, page 1051). It is at the discretion of the treating physician to determine the appropriate frequency of monitoring for individual patients. Subsequent monitoring by PCR can be performed on peripheral blood samples, although using marrow samples is a more sensitive monitoring technique and may indicate earlier signs of relapse. For patients with PCR-negative results after consolidation, ATRA maintenance (a 1- to 2-year course, which may be combined with 6-mercaptopurine and methotrexate) may be a reasonable approach, particularly for high-risk patients. For patients with low-risk disease experiencing molecular remission at completion of consolidation, clinical experience indicates that the risk of relapse is low; thus, PCR monitoring in these patients may be more appropriate in the context of a clinical trial.

For patients undergoing maintenance therapy, periodic monitoring is recommended for up to 2 years during maintenance to detect molecular relapse in patients with intermediate- or high-risk disease. At the current level of test sensitivity and specificity, a change in status from PCR-negative to PCR-positive should be confirmed through analysis of bone marrow samples in a reliable laboratory within 2 to 4 weeks. If molecular relapse is confirmed by a second positive test, patients should be treated for relapsed disease. If the second test is negative, maintenance therapy and frequent monitoring (eg, every 3 months for up to 2 years) may be considered to ensure that the patient remains PCR-negative. Testing should ideally be performed in the same laboratory to maintain a consistent level of assay sensitivity. For patients who develop cytopenias and have negative PCR results, a bone marrow biopsy is recommended to assess for new cytogenetic abnormalities, because secondary myelodysplastic syndromes and AML can rarely occur after treatment for APL.

Conclusions

These NCCN Guidelines Insights for AML highlight key updates to the management of patients with APL, focusing on the addition of a nonchemotherapy regimen as a treatment option in patients with low- to intermediate-risk disease, and providing guidance on postconsolidation maintenance strategies for APL. Although these guidelines updates are derived from evaluation of the most current available evidence at the time of the annual panel meeting, the NCCN AML Panel recognizes that guidelines updates are an iterative process given the rapidly evolving field of cancer research. To provide optimal disease management strategies for each patient, physicians must use their clinical judgment when interpreting the recommendations put forth in the guidelines. The panel continues to emphasize the importance of participation in prospective clinical trials when possible and

appropriate. Clinicians are encouraged to consult the full version of the NCCN Guidelines for AML (to view the most recent version of these guidelines, visit NCCN.org).

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NCCN Categories of Evidence and Consensus

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

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

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

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

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

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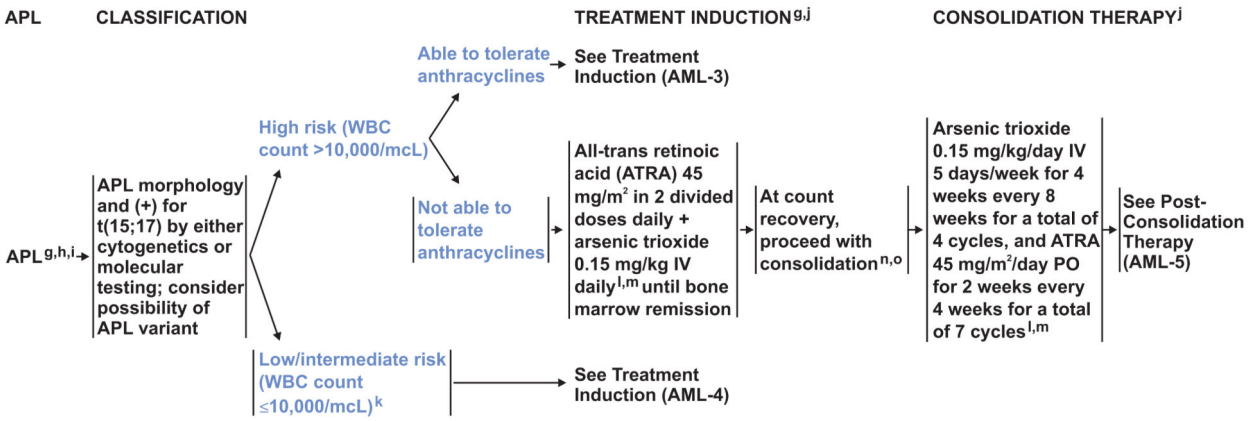
Posttest Questions

1. True or False: Although APL is a curable subtype of AML, hemorrhagic events caused by severe coagulopathy remain a primary cause of early death in these patients.
   - **a.** True
   - **b.** False
2. For patients with low- or intermediate-risk APL, which of the following induction treatment regimens are included in the NCCN Guidelines?
   - **a.** ATRA + daunorubicin
   - **b.** ATRA + cytarabine (AIDA regimen)
   - **c.** ATRA + arsenic trioxide
   - **d.** All of the above
3. True or False: Current published studies show that all patients with APL who experience molecular remission (PCR-negative status) after consolidation benefit from maintenance therapy.
   - **a.** True
   - **b.** False



[g]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 trial with consolidation from another.

[h]Therapy-related APL is treated the same as de novo APL.

[i] In patients with clinical and pathologic features of APL, start ATRA upon first suspicion of APL without waiting for genetic confirmation of the diagnosis. Early initiation of ATRA may prevent the lethal complication of bleeding. If cytogenetic and molecular testing do not confirm APL, discontinue ATRA and continue treatment as for AML.

[j]Monitor for APL differentiation syndrome and coagulopathy; see Supportive Care (AML-C 2 of 2).

[k]New data suggest similar outcomes in patients with low or intermediate risk.

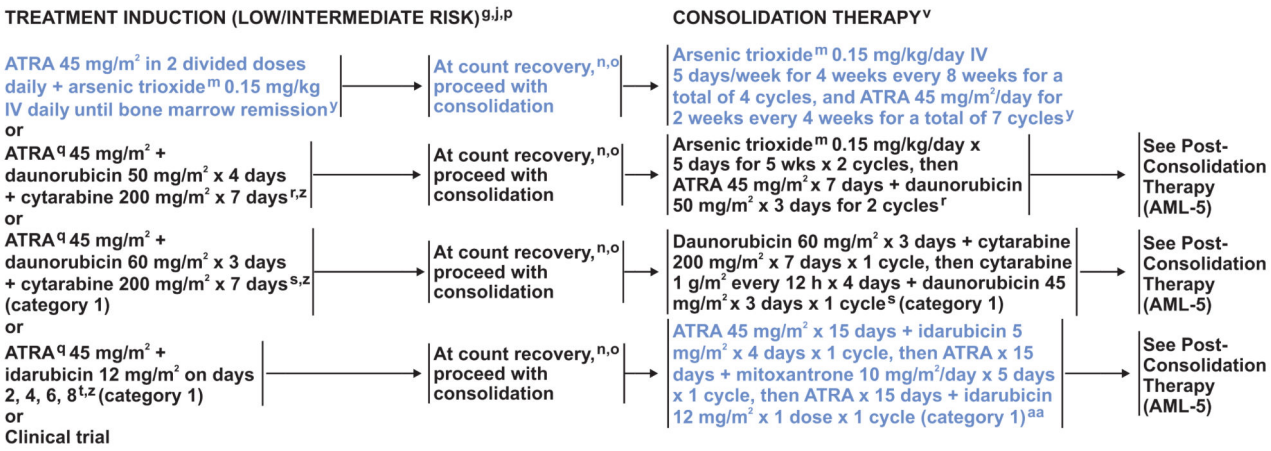
[l]Shen ZX, Shi ZZ, Fang J, et al. All-trans retinoic acid/As2O3 combination yields a high quality remission and survival in newly diagnosed acute promyelocytic leukemia. Proc Natl Acad Sci USA 2004;101(15):5328-35.

Ravandi F, Estey E, Jones D, et al. Effective treatment of acute promyelocytic leukemia with all-trans-retinoic acid, arsenic trioxide, and gemtuzumab ozogamicin. J Clin Oncol 2009;27:504-510.

[m]See Arsenic trioxide monitoring, Supportive Care (AML-C 2 of 2).

[n]Premature morphologic and molecular assessment (day 10-14 marrow) can be misleading; a nadir marrow is not recommended. Patients often remain molecularly positive at the end of induction, even when the marrow shows morphologic remission. The first assessment of molecular remission should be made after consolidation.

[o]Early mortality is related to bleeding, differentiation syndrome, or infection. Persistent disease is rare. See first relapse on AML-6.



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[p]For patients with (or who develop) a high WBC count (>10,000), consider prophylactic dexamethasone to prevent differentiation syndrome.

[q]Data suggest that lower doses of ATRA (25 mg/m^2) may be used in adolescents.

[r]Powell BL, Moser B, Stock W, et al. Arsenic trioxide improves event-free and overall survival for adults with acute promyelocytic leukemia: North American Leukemia Intergroup Study C9710. Blood 2010;116:3751-3757.

[s]Ades LA, Sanz MA, Chevret S, et al. Treatment of newly diagnosed acute promyelocytic leukemia (APL): A comparison of French-Belgian-Swiss and PETHEMA results. Blood 2008;111:1078-1086.

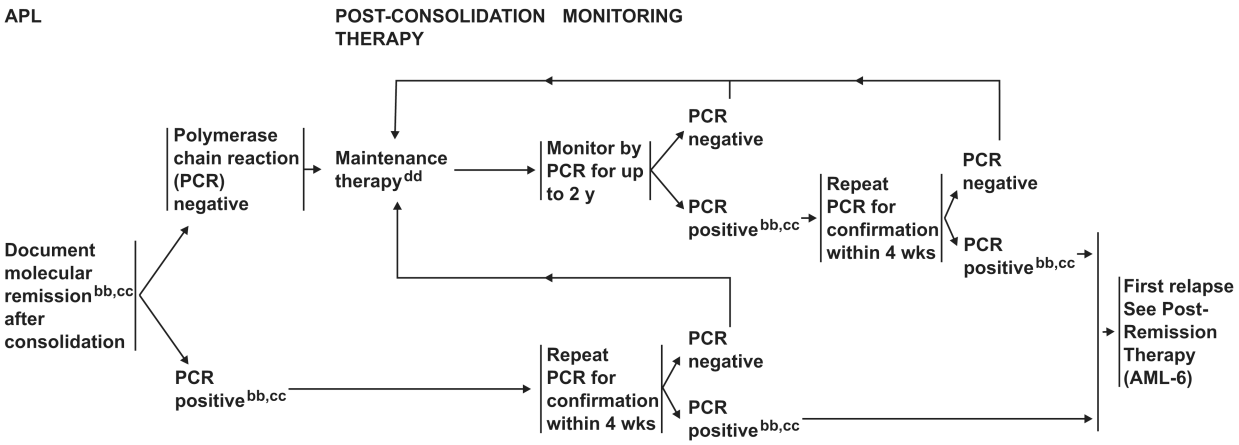
[t]Sanz MA, Montesinos P, Rayon C, et al. Risk-adapted treatment of acute promyelocytic leukemia based on all trans retinoic acid and anthracycline with addition of cytarabine in consolidation therapy for high risk patients: further improvements in treatment outcomes. Blood 2010;115:5137-5146.

[v]All regimens include high cumulative doses of cardiotoxic agents. Cardiac function should be assessed prior to each anthracycline/mitoxantrone-containing course.

[y]Lo-Coco F, Avvisati G, Orlando SM, et al. ATRA and arsenic trioxide (ATO) versus ATRA and idarubicin (AIDA) for newly diagnosed, non high-risk acute promyelocytic leukemia (APL): results of the phase III, prospective, randomized, intergroup APL0406 study by the Italian-German Cooperative Groups Gimema-SAL-AMLSG [abstract.] Blood 2012;120:Abstract 6.

[z]For patients who have rapidly escalating WBC counts or other high-risk features during course of induction therapy, see Consolidation Therapy on AML-3.

[aa]Lo-Coco F, Avvisati G, Vignetti M, et al. Front-line treatment of acute promyelocytic leukemia with AIDA induction followed by risk-adapted consolidation for adult patients younger than 61 years: results of the AIDA-2000 trial of the GIMEMA Group. Blood 2010;116:3171-3179.



[bb]PCR should be performed on a marrow sample at completion of consolidation to document molecular remission. Subsequent monitoring by PCR can be done with peripheral blood, although marrow is a more sensitive monitoring technique and may give earlier signs of relapse. Prior practice guidelines have recommended monitoring marrow by PCR every 3 mo for 2 y to detect molecular relapse. We continue to endorse this for high-risk patients, those >age 60 y or who had long interruptions during consolidation, or patients 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.

[cc]To confirm PCR positivity, a second marrow sample should be done in 2-4 weeks in a reliable laboratory. If molecular relapse is confirmed by a second positive test, treat as first relapse (AML-6).If the second test was negative, frequent monitoring (every 3 mo for 2 y) is strongly recommended to confirm that the patient remains negative. The PCR testing lab should indicate level of sensitivity of assay for positivity (most clinical labs have a sensitivity level of 10^{-4}), and testing should be done in the same lab to maintain the same level of sensitivity. Consider consultation with a physician experienced in molecular diagnostics if results are equivocal.

[dd]The majority of studies showing benefit with maintenance occurred prior to the use of ATRA and/or arsenic trioxide and/or cytarabine for consolidation. Maintenance therapy should follow the initial treatment protocol. The role of maintenance chemotherapy remains unclear, particularly for patients with low-risk disease who achieve a molecular remission at the end of consolidation. Avvisati G, Lo-Coco F, Paoloni FP, et al. AIDA 0493 protocol for newly diagnosed acute promyelocytic leukemia: very long-term results and role of maintenance. Blood 2011;117:4716-4725.