Abstract
Acute promyelocytic leukemia (APL) is remarkable for its upfront mortality rate from disseminated intravascular coagulation and its high cure rate with therapy. Although induction and consolidation regimens continue to evolve, newer approaches combine an anthracycline with or without cytarabine and the highly effective differentiating drugs all-trans retinoic acid and arsenic trioxide. Early trials showed a benefit of maintenance therapy on overall survival, although this benefit has been less clear in subsequent trials. This review assesses the differences in these trials and outlines a rational approach to maintenance therapy in APL, generally advising against maintenance in patients who underwent adequate consolidation therapy, particularly if they presented with low-risk disease (WBC < 10,000) and experienced molecular complete remission after completion of consolidation. (JNCCN 2012;10:1023–1028)

Who Benefits From Maintenance Therapy in Acute Promyelocytic Leukemia?

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Acute promyelocytic leukemia (APL) is a rare subtype of acute myeloid leukemia (AML) accounting for 10% of the 13,400 adults diagnosed with AML in the United States. The initial report by Hillestad in 1957 described it as a disease marked by a “very rapid downhill course of few weeks’ duration...[and] a severe bleeding tendency caused mainly by fibrinolysis” with a high mortality rate. This oft-quoted report stands in stark contrast to the success of modern approaches. Although early mortality from disseminated intravascular coagulation likely ranges from 15% to 20%, overall cure rates with treatment now approach greater than 80%, and APL is heralded as one of the most successful models of targeted treatment in cancer. APL is characterized by a balanced reciprocal translocation between chromosomes 15 and 17, generating a fusion transcript combining promyelocytic (PML) and retinoic acid receptor alpha (RARA) genes. This chimeric product represses the transcription of genes necessary for downstream differentiation. Early reports documented a dose-dependent cytotoxic response to anthracyclines. Subsequently, 2 highly effective, differentiating therapies—all-trans retinoic acid (ATRA) and the more active arsenic trioxide (ATO)—were introduced. Both ATRA and ATO counteract the effects of PML/RARA and thus lead to differentiation and apoptosis of the malignant cell clone.

Induction and Consolidation
If APL is suspected, administration of ATRA and plasma, cryoprecipitate, and platelet transfusions should begin immediately to reduce the risk of fatal bleeding. Once diagnosis of APL has been confirmed with molecular or cytogenetic testing for the t(15;17) translocation, simultaneous administration of ATRA and anthracycline-containing chemotherapy is currently standard induction. Complete remission rates of 90% to 95% are reported with this regimen, and primary resistance is rare if it exists at all. Outstanding questions include whether adding cytarabine confers benefit and the possibility of combining ATO with ATRA to allow avoidance of chemotherapy, at least in patients with low-risk disease (WBC count < 10,000).

Consolidation therapy involves at least 2 further cycles of anthracycline-containing chemotherapy and achieves molecular remission rates of 95%. Standard practice is including ATRA in consolidation, because

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historical comparisons suggest reduced relapse risk when used in conjunction with chemotherapy. Evidence has emerged that in high-risk patients (WBC count > 10,000) younger than 60 years, cytarabine and ATRA may have a synergistic effect.\(^1,5\) The US Intergroup reported that patients randomized to 2 courses of ATO before consolidation had superior event-free and overall survivals. However the control arm had significantly lower survival, leading some to question the relevance of the study.\(^7\)

**Maintenance Therapy**

Maintenance refers to postconsolidation treatment with the goal of improving relapse-free survival. It is generally less intensive than induction and consolidation regimens. The benefit of maintenance therapy is directly related to preceding therapy. It follows then that as induction and consolidation become more effective and consequently cure a greater proportion of patients, the effect of maintenance will diminish. In APL, 5 trials have been performed investigating the benefit of maintenance versus observation, with 2 showing benefit and 3 no benefit. This article briefly discusses these trials (Table 1), discusses reasons for their differences, and attempts to provide a rational approach to maintenance therapy.

**Early Studies in the Pre-ATRA Era**

Maintenance therapy was suggested to have benefit in the pre-ATRA era by 2 retrospective studies using 6-mercaptopurine (6-MP) and methotrexate (MTX) after anthracycline induction.\(^8,9\) These observations were not supported in the early Gruppo Italiano Malattie Ematologiche dell’Adulto (GIMEMA) pilot study in which 257 patients with newly diagnosed APL were randomly assigned to receive induction with idarubicin (IDA) or lower-dose IDA combined with cytarabine (Ara-C) followed by consolidation with cycles of Ara-C and IDA; mitoxantrone and etoposide (VP-16); and finally IDA, Ara-C, and oral 6-thioguanine (6-TG). Patients still experiencing complete remission after consolidation were randomized to observation or maintenance consisting of daily 6-MP and MTX each week for 2 years. With long-term follow-up, 60% and 55% of patients experienced relapse in the observation and maintenance groups, respectively (\(P = \text{not significant}\)). At 7 years from randomization, disease-free survival was 38% for observation and 43% for maintenance regardless of the regimen used for induction. Overall survival rates were 61% for those assigned to observation and 51% for those assigned to maintenance.\(^10\)

**Positive Studies in ATRA Era**

The benefit of maintenance was shown in the North American Intergroup and the European APL Group Experience. In the former, 350 patients were randomly assigned to receive induction with ATRA or daunorubicin (DNR) plus cytarabine. Consolidation involved a cycle identical to induction followed by a cycle of high-dose Ara-C and DNR. Patients still experiencing complete remission after these 2 cycles were randomly assigned to maintenance with ATRA or observation. Five-year disease-free survival rates based on maintenance randomization were 36% for observation and 61% for ATRA (\(P < .0001\)).\(^11,12\)

In the European APL93 study, 576 patients were randomly assigned to DNR either concurrent with ATRA or after ATRA. Patients experiencing complete remission received 2 additional cycles of DNR and Ara-C, then randomized for maintenance to no treatment, intermittent ATRA for 2 years, continuous low-dose 6-MP and MTX for 2 years, or both ATRA and 6-MP/MTX for 2 years. Long-term follow-up revealed a 10-year cumulative incidence of relapse of 43.2% for no maintenance, 33% for ATRA only, 23.4% for 6-MP and MTX only, and 13.4% for ATRA and 6-MP/MTX (\(P < .001\)). These results were not affected by the induction arm. The effect of maintenance was more pronounced in patients with WBC counts higher than 5 \(\times\) 10\(^9\)/L with a 10-year cumulative incidence of relapse of 68.4% (no maintenance), 53.1% (ATRA alone), 32.8% (DNR and Ara-C chemotherapy alone), and 20.6% (ATRA with DNR and Ara-C chemotherapy) than in patients with lower WBC counts, in whom 10-year cumulative incidence of relapse rates were 29.2%, 22.9%, 21.0%, and 11.5%, respectively.

An increased risk of relapse in patients who received maintenance treatment for less than 1 year was also seen, suggesting that treatment should continue for longer than a year, although these patients may have been at higher risk of relapse independent of duration of maintenance.\(^13,14\) Subsequently, the APL93 data were combined with data from APL2000, in which all patients received ATRA and 6-MP/MTX. Multivariate analysis revealed that receiving combined maintenance treatment was the strongest prognostic factor for cumulative incidence
Table 1  Trials Comparing Maintenance Therapy and Observation for APL

<table>
<thead>
<tr>
<th>Group</th>
<th>Induction</th>
<th>Cycle 1</th>
<th>Consolidation</th>
<th>Cycle 2</th>
<th>Cycle 3</th>
<th>Total Anthracyline</th>
<th>Maintenance</th>
<th>Outcome (%)</th>
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<tbody>
<tr>
<td><strong>GIMEMA LAP0389</strong></td>
<td>IDA, 10 mg/m² days 1–6</td>
<td>IDA, 5 mg/m² and Ara-C, 1 g/m² both days 1–4</td>
<td>MITX, 10 mg/m² and VP-16, 100 mg/m² days 1–5</td>
<td>IDA, 5 mg/m² day 1 and Ara-C, 150 mg/m² and 6-TG, 70 mg/m² both days 1–5</td>
<td>IDA, 73–85 mg/m² + 50 mg/m² MITX</td>
<td>Observation</td>
<td>7-y DFS: 38</td>
<td>7-y OS: 61</td>
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<td></td>
<td>or IDA, 12 mg/m² days 1–4</td>
<td>or Ara-C, 200 mg/m² days 1–7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6-MP, 1 mg/kg/d + MTX, 0.25 mg/kg/wk for 2 y</td>
<td>7-y DFS: 38</td>
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<tr>
<td><strong>North American Intergroup APL</strong></td>
<td>ATRA, 45 mg/m²/d or DNR, 45 mg/m² days 1–3 and Ara-C, 100 mg/m² days 1–7</td>
<td>ATRA, 45 mg/m²/d or DNR, 45 mg/m² days 1–3 and Ara-C, 100 mg/m² days 1–7 (same as first cycle)</td>
<td>DNR, 45 mg/m² days 1–2 and Ara-C, 2 mg/m² days 1–4</td>
<td>None</td>
<td>DNR, 90 mg/m² vs. 360 mg/m²</td>
<td>Observation</td>
<td>5-y DFS: 36</td>
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<td></td>
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<td>ATRA, 45 mg/m²/d for 1 y</td>
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<td><strong>European APL93 Group</strong></td>
<td>ATRA, 45 mg/m²/d → DNR, 60 mg/m² days 1–3 and Ara-C, 200 mg/m² days 1–7 or concurrent ATRA and DNR + Ara-C</td>
<td>DNR, 60 mg/m² days 1–3 and Ara-C, 200 mg/m² days 1–7</td>
<td>DNR, 45 mg/m² days 1–3 and Ara-C, 1 g/m² per 12 h days 1–4</td>
<td>None</td>
<td>DNR, 495 mg/m²</td>
<td>Observation</td>
<td>10-y CIR: 43.2</td>
<td>10-y EFS: 51.4</td>
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<tr>
<td><strong>AIDA 0493</strong></td>
<td>ATRA, 45 mg/m² + IDA, 12 mg/m² days 2, 4, 6, and 8</td>
<td>IDA, 5 mg/m² + Ara-C, 1 g/m² days 1–4</td>
<td>MITX, 10 mg/m² + VP-16, 100 mg/m² days 1–5</td>
<td>IDA, 5 mg/m² day 1 and Ara-C, 150 mg/m² and 6-TG, 70 mg/m² both days 1–5</td>
<td>IDA, 73 mg/m² + MTX, 50 mg/m²</td>
<td>Observation</td>
<td>12-y DFS: 69.1</td>
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<td>ATRA, 45 mg/m² of 15 d every mo for 2 y</td>
<td>10-y CIR: 33</td>
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<td></td>
<td>6-MP, 90 mg/m²/d + MTX, 15 mg/m²/wk for 2 y</td>
<td>10-y CIR: 23.4</td>
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<td></td>
<td>ATRA + 6-MP + MTX for 2 y</td>
<td>10-y CIR: 13.4</td>
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<tr>
<td><strong>JALSG APL97</strong></td>
<td>ATRA, 45 mg/m² or IDA, 12 mg/m² days 1–2 and Ara-C, 80 mg/m²/d days 1–5</td>
<td>ATRA, 45 mg/m² + IDA, 12 mg/m² days 1–2 and Ara-C, 200 mg/m² days 1–5</td>
<td>Ara-C, 140 mg/m² and VP-16, 100 mg/m² days 1–5 + DNR, 50 mg/m² days 1–3</td>
<td>Ara-C, 140 mg/m² and VP-16, 100 mg/m² days 1–5 + DNR, IDA 12 mg/m² days 1–3</td>
<td>Ara-C, 60–72 mg/m², MITX, 21 mg/m², DNR, 150 mg/m²</td>
<td>Observation</td>
<td>12-y DFS: 67.6</td>
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<tr>
<td></td>
<td>or ATRA + IDA, 12 mg/m²/d</td>
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<td></td>
<td></td>
<td></td>
<td>Alternating ATRA and DNR + Ara-C for 2 y</td>
<td>6-y DFS: 64.8</td>
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<td>days 1–2 and Ara-C, 80 mg/m²/d days 1–5</td>
<td>or ATRA + IDA, 12 mg/m²/d days 1–3 and Ara-C, 100 mg/m²/d days 1–5</td>
<td>MITX, 7 mg/m² and Ara-C, 200 mg/m² days 1–5</td>
<td>Ara-C, 140 mg/m² and VP-16, 100 mg/m² days 1–5 + DNR, 50 mg/m² days 1–3</td>
<td>Ara-C, 140 mg/m² and VP-16, 100 mg/m² days 1–5 + DNR, 50 mg/m² days 1–3</td>
<td>Observation</td>
<td>6-y DFS: 79.8</td>
<td>6-y OS: 98.8</td>
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<td>or</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Intensified maintenance*</td>
<td>6-y DFS: 63.1</td>
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</table>

Abbreviations: 6-MP, 6-mercaptopurine; 6-TG, 6-thioguanine APL, acute promyelocytic leukemia; Ara-C, cytarabine; ATRA, all-trans retinoic acid; CIR, cumulative incidence ratio; DNR, daunorubicin; DFS, disease-free survival; EFS, event-free survival; IDA, idarubicin; MITX, mitoxantrone; MTX, methotrexate; OS, overall survival; VP-16, etoposide.

*Intensified maintenance consisted of the following: Ara-C + DNR + 6-MP; Ara-C + MITX; Ara-C + VP-16 + vindesine; Ara-C + aclarubicin + 6-MP; Ara-C + DNR + 6-MP; and Ara-C + VP-16 + etoposide.
of relapse, event-free survival, and overall survival in patients with a WBC count of 10,000 to 50,000/mcL, and for event-free survival in patients with a WBC count greater than 50,000/mcL. Outcomes in these patients were similar to those in low-risk patients with a WBC count less than 10,000/mcL.\[13\]

**Negative Studies in the ATRA Era**

Two randomized trials of maintenance were performed in patients in molecular remission (negative for PML/RARA) after consolidation. In the Japan Adult Leukemia Study Group (JALSG) APL97 study,\[16\] 283 patients received induction therapy consisting of ATRA alone if leukocyte counts were less than 3.0 × 10^9/L and APL cells less than 10^7/L at start of therapy; ATRA with IDA and Ara-C if leukocyte counts were between 3.0 × 10^9/L and 10.0 × 10^9/L and APL cells greater than 10^9/L; or ATRA with IDA and Ara-C at a different dosing schedule if leukocyte counts were 10.0 × 10^9/L or greater. After complete remission, patients received 3 courses of consolidation consisting of mitoxantrone and Ara-C; VP-16 and DNR; and Ara-C and IDA. After consolidation, patients experiencing molecular remission were randomized to 6 courses of intensified maintenance chemotherapy every 6 weeks or observation. Maintenance involved courses of Ara-C, DNR, and 6-MP; Ara-C and mitoxantrone; Ara-C, VP-16, and vindesine; and Ara-C, aclacinomicin, and 6-MP. The fifth and sixth courses were the same as the first and third, respectively.

Results of this study showed that disease-free survival at 6 years was 63.1% for patients assigned to maintenance chemotherapy and 79.8% for those assigned to observation (P = .2).\[16\] Predicted 6-year overall survival in the observation group was 98.8%, which was significantly higher than the 86.2% predicted in the intensified maintenance group (P = .014). The greater benefit of observation in terms of overall survival compared with disease-free survival was thought to be from a higher second complete remission rate (76% vs. 54%) and longer second complete remission duration. In addition, 8 patients in the chemotherapy group showed late relapse occurring after 3 years of continuous complete remission, whereas no patients in the observation group showed late relapse (P = .006). Although no therapy-related mortality occurred among patients treated with maintenance therapy, one patient developed therapy-related myelodysplastic syndromes and another developed AML during their first complete remission of APL versus none in the observation group.\[16\]

In the Italian AIDA 0493 study, 828 patients received induction with ATRA and IDA. Patients who were in hematologic complete remission received 3 cycles of consolidation: IDA and Ara-C; then mitoxantrone and VP-16; then IDA, Ara-C, and 6-TG. Initially, patients in molecular complete remission after 3 consolidation cycles were randomized to 6-MP and MTX; ATRA alone; alternating 6-MP/MTX and ATRA; and observation, with each of the treatments continuing for 2 years. After 318 patients had been randomized, the protocol was amended so that patients were randomized only to the 2 ATRA-containing options, given that disease-free survival appeared better with these than with observation or 6-MP/MTX without ATRA. However, with longer follow-up, 12-year disease-free survival rates were similar in the 4 groups: 70.4%, 69.0%, 67.6%, and 69.1%. No difference was seen in the ATRA versus ATRA and chemotherapy group after maintenance amendment.\[17\]

**Differences in Trials**

Multiple important confounding factors complicate comparison of these 5 trials. First, the studied populations were different. In the North American and European trials, both the diagnosis of APL and assessment of complete remission after consolidation were determined through morphologic review; molecular or cytogenetic confirmation of t(15;17) was not required. This contrasts with the AIDA0493 and JALSG APL97 studies, which required molecular or cytogenetic confirmation. This difference may have enriched the North American and European trials with other subtypes of AML at diagnosis or with patients not in molecular remission at maintenance therapy. Patients with other subtypes of AML or with APL showing persistent disease may have benefited from maintenance therapy and could have contributed to the positive results in these trials.

Second, in the 3 studies that did not show a benefit of maintenance, 3 cycles of anthracycline-based consolidation were used versus 2 cycles in the positive studies.

Third, the predominant anthracycline used in the negative studies was IDA; those that showed maintenance benefit used DNR. When dose equivalency between IDA and DNR is calculated between the trials (assuming 1 mg/m^2 IDA = 5 mg/m^2 DNR), the negative trials typically used between 110% and 130% of the anthracycline dose in the positive stud-
ies. It seems likely that the higher anthracycline dose alone or in concert with choosing IDA over DNR may have eliminated the need for maintenance.

**Adverse Effects**

The JALSG APL97 trial clearly established the adverse effect of intensive maintenance chemotherapy in patients testing negative for the PML/RARA transcript at the end of consolidation by showing that intensive maintenance does not improve disease-free survival and can actually worsen overall survival compared with observation alone. It raised the possibility that maintenance therapy can select for drug resistance, making a second complete remission difficult to achieve after relapse, and that it can increase the incidence of therapy-related leukemia. In the less-intensive therapies studied, including 6-MP and MTX with or without ATRA, the APL97 study primarily documented cytopenias and liver enzyme elevation, with 45% of patients experiencing toxicity requiring dose reduction. Of the 401 patients randomized to no maintenance, ATRA, ATRA with DNR and Ara-C, or DNR and Ara-C chemotherapy alone, 6 fatal cases of sepsis occurred, 6 patients were admitted for febrile neutropenia, and 3 cases of nonfatal Pneumocystis jiroveci were seen. In a Japanese case series of 10 patients, a less-intensive regimen of ATRA, 6-MP, and MTX was used for maintenance, and no patients were able to tolerate therapy, also suggesting an ethnicity-related effect. Dose reductions occurred in all cases, and there was at least one therapy-related death.

**Maintenance Therapy in the ATO Era**

Recently, data on maintenance from the North American Leukemia Intergroup Protocol C9710, which incorporated ATO as part of consolidation, was presented in abstract form at the 2011 ASH Annual Meeting. In this study, 481 patients with untreated APL were induced with ATRA, cytarabine, and DNR, and subsequently randomized to proceed to consolidation or receive 2 cycles of ATO followed by 2 cycles of ATRA and DNR. Patients in molecular complete remission after completion of consolidation therapy were randomized to either 1 year of ATRA maintenance alone or with 6-MP and oral MTX. The trial initially included an observation arm, but unfortunately this was closed shortly after long-term reports from the North American Intergroup study and European APL93 Group were published showing benefit with maintenance therapy. The 6-year disease-free survival was not statistically different for the 2 maintenance arms of ATRA alone versus ATRA with DNR and Ara-C at 79% and 87%, respectively (P = .056); a slight trend was seen, however, toward combination maintenance. Overall survival was not significantly different between ATRA, and ATRA with DNR and Ara-C maintenance at 92% and 95%, respectively (P = .28). In addition, results were published recently of a single-arm trial of 82 patients with APL who received induction therapy with ATRA and ATO with or without gemtuzumab, an anti-CD33 monoclonal antibody conjugated to the toxin calicheamicin, and 6 months of consolidation with ATO. Complete remission rates for low- and high-risk patients were 95% and 81%, respectively. After a median follow-up of 99 weeks, only 3 patients had experienced relapse and all were from the high-risk category.

**Rational Approach to Maintenance Therapy**

Under “Post-Consolidation Therapy” and “Monitoring” in the Acute Promyelocytic Leukemia section of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for AML (available online, in these guidelines, at NCCN.org [AML-5]), a footnote states that the role of maintenance chemotherapy remains unclear, particularly for patients with low-risk disease who achieve a molecular remission at the end of consolidation...The majority of studies showing benefit with maintenance occurred prior to the use of ATRA and/or arsenic trioxide and/or cytarabine for consolidation. Trials are evaluating benefits of maintenance in this group.

The authors agree with this, particularly because as ATO has been incorporated into induction and consolidation regimens, it has become increasingly unclear how to best use maintenance therapy, if at all. The ATO trials described suggest that incorporation of ATO in the treatment of APL may obviate the need for maintenance therapy. Optimally, every patient diagnosed with APL will be treated as part of a clinical trial to systematically answer the question of maintenance benefit. However, for those treated off-trial with protocols involving ATRA/ATO and at least 2 cycles of anthracycline-based consolidation, one may consider monitoring those with low-
intermediate-risk disease who have experienced molecular remission after consolidation without exposing them to the risks of maintenance therapy, because the benefit is questionable, while offering those with high-risk disease additional therapy with either ATRA and combined DNR and Ara-C, recognizing that supporting studies for this strategy are lacking. One must also bear in mind that information obtained after treatment begins is typically more prognostically relevant than pretreatment data. Thus, patients who begin with low-risk disease (WBC count < 10,000) but have minimal residual disease after completion of consolidation should be placed in the high-risk group. The reason for offering maintenance is that the presumed benefit (prevention of relapse) outweighs the presumed risk. This argument would be strengthened if effective salvage regimens did not exist at relapse. However, in a group of patients treated according to the AIDA protocol who experienced relapse, second molecular complete remission was achieved in 86%, with 2-year survival from time of relapse of 92%. Results of the North American Leukemia Intergroup study S0521 are eagerly awaited, in which patients with low-/intermediate-risk disease receiving the same induction and intermediate regimens as in the North American Leukemia Intergroup Protocol C9710 are assigned to either observation or maintenance therapy.

References