CLINICAL OBSERVATIONS, INTERVENTIONS, AND THERAPEUTIC TRIALS

Molecular Remissions Induced by Liposomal-Encapsulated All-Trans Retinoic Acid in Newly Diagnosed Acute Promyelocytic Leukemia

By Elihu H. Estey, Francis J. Giles, Hagop Kantarjian, Susan O’Brien, Jorge Cortes, Emil J Freireich, Gabriel Lopez-Berestein, and Michael Keating

All-trans retinoic acid administered orally (oral ATRA) may not regularly lead to either molecular complete remissions (CRs) or prolonged hematologic CRs (HCR) unless combined with chemotherapy. Because serum retinoin concentrations are higher, and maintained longer, after use of liposomal-encapsulated ATRA (lipoATRA) rather than oral ATRA, we investigated lipoATRA monotherapy in newly diagnosed acute promyelocytic leukemia (APL). Patients received lipoiATRA 90 mg/m² every other day for remission induction. The same dose was given 3 times a week until 9 months had elapsed from HCR date. Treatment then stopped. Chemotherapy (idarubicin 12 mg/m² daily days 1-2 for 2 courses) was to be added only if 2 polymerase chain reaction (PCR) tests, performed 2 weeks apart, were positive at 3, 6, or 9 months from HCR date. The sensitivity level of the PCR was 10⁻⁴. We treated 18 patients (median age, 54 years; median white blood cell [WBC] count 4,500/µL). The HCR rate was 12/18 (67%, 95% confidence interval [CI], 41% to 87%). This rate was similar to that we observed in a previous study using oral ATRA + idarubicin. Nine of 10 patients studied at HCR date were PCR-positive. Subsequently, however, overall (+/− idarubicin) rates of PCR positivity were 0/12 at 3 months, 1/10 at 6 months, 1/7 at 9 and 12 months, and 0/4 at 15 to 17 months. Idarubicin has been added in 3 patients, with this addition occurring at 6 months in 2 patients and at 9 months in 1 patient. Among patients who had not received idarubicin when the PCR was evaluated, 0 of 12 were PCR-positive at 3 months, 1 of 10 was positive at 6 months, 1 of 6 was positive at 9 months, 0 of 4 were positive at 12 months, and 0 of 3 were positive at 15 to 17 months. Morphologic APL has recurred in 1 patient, with a median follow-up time of 13 months in the 11 patients remaining in first CR. The median follow-up time is 9 1/2 months (range, 3 to 17) in the 9 patients who have received only lipoATRA and who remain PCR-negative and in first CR. Our data suggest that lipoATRA is an effective means of producing molecular CR in newly diagnosed APL.

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of hematologic CR. Herein we report results in the first 18 patients.

MATERIALS AND METHODS

Eligibility required that patients (1) have untreated APL, (2) not be pregnant, and (3) be logistically capable of receiving lipoATRA for 10 months, this being the total treatment duration as described below. Between August 21, 1997, when the first patient was enrolled on study, and December 9, 1998, when the 18th was enrolled, we saw 20 patients with untreated APL. One did not qualify because she was pregnant, and the second did not qualify because she could not receive lipoATRA in her native Venezuela. Both patients presented with white blood cell (WBC) counts > 10,000/µL; both received oral ATRA + idarubicin with the first dying on day 4 of treatment of intracranial hemorrhage and the second now remaining in CR for 4 months. The diagnosis of APL required either cytogenetic or molecular (PCR) test evidence of the (15-17) translocation. Such evidence was obtained in 17 of the 18 patients reported here. The 18th patient had typical microgranular APL, accompanied by disseminated intravascular coagulation (DIC), but specimens were not sent for cytogenetic or PCR studies. The patient died on day 2 of intracranial hemorrhage and, although technically ineligible, we include him in the results because of the high probability that the (15-17) and/or PML-RARα rearrangement was present.

Induction therapy consisted of lipoATRA 90 mg/m² administered intravenously (IV) over 30 minutes every other day until standard criteria for hematologic CR were met.11 Hematologic CR refers to a marrow with < 5% blasts and < 8% promyelocytes without morphologically abnormal promyelocytes. Additionally, the neutrophil and platelet counts must be above 1,000 and 100,000/µL, respectively. Patients received corticosteroids in the event of suspected ATRA syndrome and were transfused to maintain the platelet count > 30,000/µL and the fibrinogen > 180 mg/dL; heparin was not administered. Once in hematologic CR, patients continued to receive lipoATRA at 90 mg/m², now every Monday, Wednesday, and Friday. Twenty-five percent dose decreases were mandated for ≥ grade 3 National Cancer Institute (NCI) criteria toxicity. A PCR test, performed at a level of $10^3$, was obtained 3, 6, and 9 months from CR date. If these were negative, lipoATRA was continued until the 9-month time point, when all therapy was discontinued. If the PCR test was positive at 3, 6, or 9 months, another PCR was performed at the same level 2 weeks later. If this test was also positive, idarubicin (12 mg/m² daily × 2 days for 2 courses given 4 to 5 weeks apart) was added and lipoATRA continued. If the repeat test was negative, chemotherapy was not added. If after 2 courses of idarubicin + lipoATRA the PCR remained positive, patients received arsenic trioxide. In sum, patients were to receive chemotherapy only if they were PCR-positive at $10^{-3} \times 2$ at 3, 6, or 9 months from hematologic CR date. Otherwise, they received only lipoATRA, stopping therapy 9 months from this date. Thereafter, they were followed with PCR tests every 3 months. To evaluate the accuracy of our PCR test, we sent 7 samples (6 PCR-negative, 1 PCR-positive) from patients on this study to Dr Francesco Lo Coco (University La Sapienza, Rome, Italy) of the GIMEMA group, who repeated the PCR analyses without knowledge of our results. Dr Lo Coco confirmed our results in all 7 cases. Morphologic examination of the bone marrow and routine complete blood counts (CBCs) were performed when PCR tests were obtained. Pharmacology studies were not performed.

The use of lipoATRA monotherapy in a disease in which oral ATRA + anthracyclines produce a substantial long-term disease-free survival rate was controversial. To monitor the study and stop it expeditiously if results were worse than in patients previously given oral ATRA + idarubicin at M.D. Anderson,11 we used the multiple outcome statistical design of Thall et al.12 In the formulation we used, the study would stop if, based on results as a patient was about to be accrued, the probability was > .90 that the hematologic CR rate with lipoATRA was less than the rate we had observed with oral ATRA + idarubicin (34 of 44 = 77%). Early termination would also occur if the probability was > .95 that, among patients achieving hematologic CR, the percent remaining alive in such CR 12 months from CR date was less than the comparable percent with oral ATRA + idarubicin (28 of 34 = 82%). These stopping rules were such that if the true hematologic CR rate was in fact 57% (20% lower than historical), there was 94% probability that the study would stop after a median of 12 patients had been enrolled. Similarly, if, among patients achieving hematologic CR, the true proportion remaining alive in CR at 12 months was 62% (again 20% lower than historical), there was 82% probability that the study would stop after a median of 19 patients had entered CR. If early stopping did not occur, we planned to accrue 50 patients. However, accrual of this number would require another 3 years not counting follow-up time, leading us to report our current results.

RESULTS

The median age of the 18 patients was 54 years (range, 11 to 72). Three patients were largely bedridden (Zubrod performance status 3) at presentation, 2 because of dyspnea associated with bilateral densities on chest x-ray, and 1 because of a depressed level of consciousness due to a cerebellar hemorrhage. The median WBC count at presentation was 4,500/µL (range, 400 to 54,000, 6 patients with > 10,000), and the median platelet count was 28,000/µL (range, 7 to 133,000). Fourteen of the 18 patients had the t(15;17) translocation on standard (minimum of 20 metaphases counted) cytogenetic analysis; additional changes were found in 4 of the 14. In 3 patients the karyotype was normal, but the PCR test was positive. The final patient had typical microgranular APL, but no samples for cytogenetic or PCR testing were sent (see Materials and Methods). PCR testing was performed at presentation in 16 patients: 7 had the “short,” 8 the “long,” and 1 the “variable” isoform.

Induction results. The hematologic CR rate was 12/18 (67%; 95% CI, 41% to 87%). Patients were generally treated as outpatients and did not have daily blood counts once 2 to 3 weeks had elapsed from beginning therapy. Bearing this in mind, the median time to achieve CR was 34 days (range, 22 to 64). Four of the 6 failures died of hemorrhage. Three died of central nervous system (CNS) hemorrhage in the first 4 days after starting lipoATRA, and the fourth died 26 days after starting therapy of complications of pulmonary hemorrhage that also occurred in the first week of therapy. The presenting WBC counts in the 4 who died of hemorrhage were between 16,800 and 54,000/µL; one of the 4 had a cerebellar hemorrhage at presentation and died of a repeat hemorrhage. The fifth patient who did not achieve CR presented with bilateral lower limb venous thromboses. Because these appeared to worsen during the first 3 days of treatment, he was given idarubicin instead of lipoATRA, but died 3 weeks later. The final patient who failed to attain CR developed acute myocardial failure, confirmed by echocardiogram, 1 day after beginning therapy and died 1 day later. The patient had a history of coronary artery disease and had been taking an angiotensin converting enzyme inhibitor that had been discontinued when lipoATRA began. Autopsy failed to show acute thrombosis or other causes of acute myocardial failure. Nine patients began treatment with significantly abnormal values for serum fibrinogen (< 180 mg/dL). Fibrinogen became consistently over this level in 7 of the 9 at a median of 4
days after beginning lipoATRA (range, 1 to 11). In the remaining 2 who died, one of hemorrhage, the fibrinogen remained <180 at death, which occurred on days 2 and 3, respectively. Eight patients had significantly elevated prothrombin times (PT >15 seconds) before treatment. The PT decreased below this value in 3 of the 8 at 2, 2, and 10 days into treatment. In the remaining 5, all of whom died, 4 of hemorrhage, the PT remained >15 seconds at death or last follow-up, which occurred at 2, 3, 3, 7, and 19 days, respectively.

The most obvious difference between the 12 patients who did and the 6 who did not achieve CR was the presenting WBC count ($P = .002$, Mann-Whitney test). The CR rate was 11/12 (92%) in patients with WBC <10,000/µL and only 1/6 (17%) in patients with higher WBC. The $P$ value (Fisher exact test) for this comparison is .004, and the 95% CI for the true difference in the 2 rates is (.24, 1.0). All 3 patients with a performance status of 5 in patients with WBC >10,000/µL had CR rates of 12/15 (80%) in patients who had a performance status <3 ($P = .02$, Fisher exact test). Neither age nor initial platelet count affected the CR rate. CR rates were 6/7 (86%) in patients with the long isoform and 4/8 if the short isoform was present ($P = .39$, Fisher exact test). There are examples of continued positivity on 2 occasions (patients 4 and 7). There are insufficient data to assess whether a particular isoform is more likely to revert to positivity on lipoATRA, the boundary for stopping the study if the CR rate was unacceptably low was not crossed; stopping after 18 patients would have required a CR rate of ≤10/18. PCR testing, at 10--4, was performed at time of hematologic CR in 10 of the 12 patients who achieved this outcome. The test was positive in 9 patients and negative in only 1.

**Results of postremission therapy.** Table 1 examines results of PCR tests performed at the indicated times. All 12 patients were PCR-negative 3 months from hematologic CR date. The 3 of these 12 whose PCR was negative at CR or not performed at CR were PCR-positive at diagnosis (patients 1 and 9) or did not have PCR testing at diagnosis, but had the t(15;17) on standard testing (patient 2). At 6 months from CR date, 8 patients were PCR-negative and 1 was positive on 2 occasions 2 weeks apart (patient 3). As specified in the protocol, idarubicin was added to lipoATRA. The PCR at 9 months from CR date (3 months after beginning idarubicin) was suboptimal, but a frank relapse occurred 1 year from CR date (Table 1). In the final patient evaluated to date at 6 months from CR date, the PCR was first positive, but was negative on repeat testing (patient 7). Nonetheless, at the attending physician’s discretion, idarubicin was added to lipoATRA, of course making it impossible to ascertain whether the negative PCR tests obtained 3 and 6 months later would have been obtained had idarubicin not been added. At 9 months from CR date, 6 patients have been evaluated having received only lipoATRA monotherapy (patients 1, 2, 4, 5, 6, and 8). One was PCR-positive × 2 and thus had idarubicin added to lipoATRA, becoming PCR-negative again 3 and 8 months later (patient 1). The remaining 5 were PCR-negative, and thus discontinued therapy. Four of the 5 have been evaluated at 12 months from CR date. Each remains PCR-negative (patients 2, 4, 5, and 6). Three of the 5 have been evaluated at 15, 15, and 17 months, with each remaining PCR-negative (patients 2, 5, and 6). Including all 12 patients (the 3 who did and the 9 who did not receive idarubicin), PCR negativity rates are 12/12 at 3 months, 8/9 at 6 months (with the 1 additional patient being positive, then negative), 6/7 at both 9 and 12 months, and 0/4 at 15 months (Table 1). Four patients are PCR-negative 6 to 8 months after stopping lipoATRA (patients 1, 2, 5, 6). Two additional patients are PCR-negative 3 months after stopping the drug (patients 4 and 7). There are insufficient data to assess whether a particular isoform is more likely to revert to positivity on lipoATRA monotherapy. Of the 2 patients who reverted to PCR positivity on 2 occasions (patients 1 and 3), 1 had the short and the other the long isoform. There are examples of continued negativity at 12 months with short or variable isoforms and at 9 months with the long isoform. The only patient who entered CR after presenting with a WBC count >10,000/µL was the patient whose PCR test reverted to positive on 1 occasion at 6 months.

**Table 1. PCR Results**

<table>
<thead>
<tr>
<th>Patient (PCR isoform)</th>
<th>PCR at CR</th>
<th>PCR at CR + 3 mo</th>
<th>PCR at CR + 6 mo</th>
<th>PCR at CR + 9 mo</th>
<th>PCR at CR + 12 mo</th>
<th>PCR at CR + 15 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (long)</td>
<td>Not done</td>
<td>Negative</td>
<td>Negative</td>
<td>Positive × 2‡</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>2 (not done)</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>3 (short)</td>
<td>Positive</td>
<td>Negative</td>
<td>Positive × 2*</td>
<td>Negative</td>
<td>Positive</td>
<td>Positive (marrow relapse)</td>
</tr>
<tr>
<td>4 (short)</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Too early</td>
</tr>
<tr>
<td>5 (short)</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>6 (variable)</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>7 (long)</td>
<td>Positive</td>
<td>Negative</td>
<td>Positive × 1, Negative × 1†</td>
<td>Negative</td>
<td>Negative</td>
<td>Too early</td>
</tr>
<tr>
<td>8 (long)</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Too early</td>
<td>Too early</td>
</tr>
<tr>
<td>9 (long)</td>
<td>Not done</td>
<td>Negative</td>
<td>Negative</td>
<td>Too early</td>
<td>Too early</td>
<td>Too early</td>
</tr>
<tr>
<td>10 (long)</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
<td>Too early</td>
<td>Too early</td>
<td>Too early</td>
</tr>
<tr>
<td>11 (long)</td>
<td>Positive</td>
<td>Negative</td>
<td>Too early</td>
<td>Too early</td>
<td>Too early</td>
<td>Too early</td>
</tr>
<tr>
<td>12 (short)</td>
<td>Positive</td>
<td>Negative</td>
<td>Too early</td>
<td>Too early</td>
<td>Too early</td>
<td>Too early</td>
</tr>
</tbody>
</table>

*Idarubicin added to lipoATRA when PCR results known.
†Idarubicin added to lipoATRA when positive PCR result known.
‡Idarubicin added to lipoATRA when PCR results known.
LIPOSOMAL ATRA IN NEWLY DIAGNOSED APL

from CR date, but was negative on repeat testing (patient 7, discussed above).

Events (relapse by standard morphologic criteria or death in CR) have occurred in 1 of the 12 patients in Table 1 (patient 3). As mentioned above, there was morphologic reappearance of this patient’s APL after a CR of 1 year despite addition of idarubicin when the PCR reverted to positivity 6 months from CR date. A second remission was induced and has been maintained for 1 month on arsenic trioxide. Each of the remaining 11 patients in Table 1 remains in first CR, with follow-up times of 3, 3, 6, 6, 9, 13, 13, 15, 15, 17, and 17 months from hematologic CR date (median, 13 months). Idarubicin has been added in 3 of the 12 patients in Table 1 (patients 1, 3, and 7). In both patients 1 and 3, drug was added because of 2 positive PCR tests, as prescribed in the protocol, with these occurring, respectively, at 9 and 6 months from CR date. In patient 7, the decision was made by the attending physician, because of a single positive test. Among the 9 patients who have received only lipoATRA and remain PCR-negative in first CR, the median follow-up time is 9½ months (range, 3 to 17) from hematologic CR date.

Toxicity. Toxicity could not be evaluated in the 4 patients who suffered early hemorrhage. Among the remaining 14, worsening thromboses in the patient taken off lipoATRA and given idarubicin on day 4 could have been due to lipoATRA, but of course, is also a feature of APL; indeed, the patient presented with thromboses. Similarly, the case of fatal acute myocardial failure could have been due to lipoATRA, but no other stigmata of “ATRA syndrome,” eg, pericarditis, noncardiogenic pulmonary edema were present. Grade III (NCI criteria) toxicity more definitely related to lipoATRA occurred in 4 of the 14 patients who did not suffer early hemorrhage. Three of the 4 had the ATRA syndrome. These 3 had fever, dyspnea, and joint pain without alternative explanation. The fourth had pseudotumor cerebri characterized by headache and papilledema accompanied by normal mental status and a magnetic resonance imaging (MRI) scan showing no intracerebral or extracerebral masses. Steroids and 25% reduction in the lipoATRA dose were therapeutically effective, and all 4 continued to receive lipoATRA. An additional 2 of the 14 patients had grade 2 or less toxicity characterized by headache, joint pain, and dry skin. We could evaluate changes in WBC count in 13 patients. In these 13, the WBC count increased from a pretreatment median of 2,000/µL to a posttreatment median high of 15,300/µL (range up to 154,000/µL). Defining an increase as a doubling in the WBC count and a peak value >10,000/µL, an increase occurred in 9 of the 13 patients. The increase began in the first or second week of therapy and the peak occurred in the second or third week. The count returned to normal 1 to 2 weeks after the peak was reached. There was no correlation between the amount of increase in the WBC count and the occurrence of grade 3 toxicity.

**DISCUSSION**

Our study shows that lipoATRA as a single agent (“monotherapy”) has activity in newly diagnosed APL. In only 3 of 12 patients was idarubicin added, at 6, 6, and 9 months into hematologic CR, because of PCR positivity. In 1 of the 3, addition was based on 1 positive test followed by a negative test. Focusing on patients who had not received idarubicin when the PCR was evaluated in remission, 12 of 12 were PCR-negative at 3 months from hematologic CR date, 8 of 9 were PCR-negative at 6 months, 5 of 6 were negative at 9 months, 4 of 4 were negative at 12 months, and 3 of 3 were negative at 15 to 17 months. Because 9 of 10 patients tested at CR date were PCR-positive, the development of PCR negativity occurred during the first 3 months of CR.

It would obviously be useful to compare rates of PCR negativity in newly diagnosed patients after monotherapy with lipoATRA with similar rates after monotherapy with oral ATRA. It has been reported that 83% (39 of 47) of newly diagnosed patients given oral ATRA without chemotherapy for induction remain PCR-positive at time of CR, reminiscent of our data with lipoATRA. However, there are no published results of PCR tests after continued oral ATRA monotherapy in newly diagnosed patients. PCR data after oral ATRA monotherapy in relapsed APL is available in the publication by Miller et al. Thus, to compare the PCR data noted in Table 1 with those reported after oral ATRA monotherapy, we used this publication. Three of 13 patients in the study by Miller et al had previously received ATRA, with chemotherapy following in all 3. Table 2 shows that there is statistically significant evidence that the rates of PCR negativity at both 3 and 6 months from CR are higher with lipoATRA. The magnitude of the differences is also noteworthy. Thus, even at 9 months from CR date, when the P value is insignificant, the 95% exact CI for the true difference in rates is (.30, .99), indicating that there is as much evidence for a true difference of .70 in favor of lipoATRA as for no true difference, as both 0 and .70 are equidistant from the midpoint of the CI (.35).

It is conceivable that continuation of oral ATRA monotherapy in newly diagnosed APL might produce rates of PCR negativity similar to or higher than those we observed after lipoATRA monotherapy. In this context, Jurcic (personal communication, January 1999) has noted that 7 of 34 patients with newly diagnosed APL at Memorial Sloan-Kettering Cancer Center who were PCR-positive at CR date and received oral ATRA for 1 additional month before starting chemotherapy became PCR-negative before beginning the chemotherapy. If continued oral

### Table 2. Rates of PCR Negativity: LipoATRA Monotherapy Versus Oral ATRA Monotherapy

<table>
<thead>
<tr>
<th>Months From CR</th>
<th>Current Study: Newly Diagnosed Patients PCR Negative/</th>
<th>Oral ATRA: Relapsed Patients PCR Negative/</th>
<th>P Value (Fisher exact test)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients Evaluated*</td>
<td>Patients Evaluated*</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>12/12</td>
<td>0/7</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>6</td>
<td>8/9†</td>
<td>0/5</td>
<td>.003</td>
</tr>
<tr>
<td>9</td>
<td>5/6</td>
<td>0/1</td>
<td>.288</td>
</tr>
<tr>
<td>12</td>
<td>4/4</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>15</td>
<td>3/3</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

*Table includes patients who received lipoATRA without idarubicin. If all patients are considered, the rates are 12/12 at 3 months, 8/9 at 6 months (with 1 additional patient positive then negative), 6/7 at 9 months, 6/7 at 12 months and 4/4 at 15 months.

†If patient with positive then negative PCR result at 6 months is included, rate becomes 8/10 and P value = .007.
ATRA monotherapy produced a high rate of persistent PCR negativity, a low relapse rate might be expected in patients treated in this fashion. Apparently, the only studies reporting use of oral ATRA monotherapy, although without PCR data, in newly diagnosed APL are early Chinese studies. The median CR duration in such patients was 5 months, as quoted by Fenaux et al. Comparison of this result with that in our patients given lipoATRA monotherapy is confounded because the lipoATRA patients were given idarubicin if they were PCR-positive in CR, whereas the Chinese patients were not. Limiting the comparison to the lipoATRA patients who did not receive chemotherapy obviously introduces bias because these patients did not receive chemotherapy precisely because they were PCR-negative and thus thought unlikely to relapse. We are also unable to compare the oral ATRA and lipoATRA groups with respect to covariates (eg, WBC count) other than treatment that could influence CR duration.

The CR rate observed after lipoATRA (12/18, 67%) appears low when compared with the much higher rates (eg, 90%) reported in European studies administering oral ATRA without chemotherapy in newly diagnosed APL. However, the 67% CR rate was similar to the 77% rate we observed with oral ATRA + idarubicin in our immediately preceding study. In that study, we noted that the predictors of outcome of induction therapy were initial WBC count and platelet count. Based on these counts, 11 to 12 of the 18 patients given lipoATRA in the current study would have been expected to enter CR had they received oral ATRA + idarubicin, as given in the previous study (see Fig 1 in Estey et al), and 12, in fact, entered CR after lipoATRA. A similar proportion of the patients in our oral ATRA + idarubicin and lipoATRA studies had Zubrod performance status >2, and although the patients given lipoATRA were older (P = .05, Mann-Whitney test), we could not identify age as a prognostic factor in either study. This, of course, may merely reflect our small sample sizes, because older age has been associated with poorer outcome in European studies. Elevated presenting WBC count appears to be associated with a poor response to both oral ATRA and lipoATRA. The lower CR rates observed in either our oral ATRA + idarubicin or lipoATRA studies compared with the European studies may result from a higher proportion of patients with relatively high WBC counts at M.D. Anderson. Regardless, our CR rates in either study are consistent with the CR rate observed by the US Intergroup after oral ATRA or chemotherapy.19

In conclusion, single agent lipoATRA can produce PCR negativity in a high proportion of newly diagnosed APL patients induced into CR solely with this drug. This result, together with the persistence of PCR negativity, does not conform to the generally held view that addition of chemotherapy is necessary to render patients PCR-negative if induced into CR with only oral ATRA. Further follow-up will be needed to ascertain the duration of PCR negativity in our patients. Thus, the proportion of lipoATRA-treated patients who will ultimately require chemotherapy remains unknown. However, even if use of lipoATRA cannot totally obviate the need for chemotherapy in all patients, it might permit a reduction in the amount of chemotherapy needed to cure newly diagnosed APL. A randomized comparison of oral ATRA + chemotherapy, lipoATRA + chemotherapy, and lipoATRA monotherapy, as given in the current study, might be undertaken to address this issue.

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REFERENCES


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