Response

In the October 16 “News” section of the Journal, Richard Klein of the National Center for Health Statistics intended to cover only cancer-related objectives unique to women in his Stat Bite.

However, the “News” section frequently covers tobacco issues. For example, we carried an article in the October 2 issue and three articles on tobacco issues in the September 4 issue. We also carried a separate article on combined therapy for lung cancer in the September 4 issue. Tobacco is a major problem and we will continue to cover it.

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Re: Response of Aleukemic Granulocytic Sarcoma to All-trans-retinoic Acid Plus Interferon Alfa-2a

Most patients treated with continuous daily doses of all-trans-retinoic acid (ATRA) experience a progressive decline in plasma drug concentrations by day 7, and it has been suggested that this may account for the development of resistance to ATRA in patients with acute promyelocytic leukemia (1). About 20%-25% of the population will not experience such a decline (2).

Toma et al. (3) have described a patient with aleukemic granulocytic sarcoma who was treated for 1 month with ATRA given orally at a dose of 45 mg/m² per day, in two daily administrations, for 3 consecutive days per week plus interferon alfa-2a (IFN α-2a) given intramuscularly at a dose of 3 million units three times a week, followed by 12 weeks of IFN α-2a alone. The patient achieved a durable complete response. ATRA levels were measured in this patient and were said (although no data are shown) to have demonstrated “prolonged exposure to effective ATRA concentrations.”

One of these authors (4) had previously described a regimen consisting of 15 days of IFN α-2a alternating with 15 days of ATRA. Pharmacokinetics were studied in two patients and demonstrated day-15 ATRA levels to be similar to day-1 ATRA levels.

It has been previously reported that a patient with acute promyelocytic leukemia with acquired resistance to ATRA had a second response when daily recombinant human IFN α-2b was added at a dose of 5 × 10⁶ IU to continuous ATRA (5). Such a regimen is unlikely to have resulted in prolonged exposure to high plasma concentrations of ATRA.

We report here on two patients treated with a regimen of continuous oral ATRA at a dose of 150 mg/m² per day for days 1-29 followed by the same ATRA regimen combined with subcutaneous IFN α-2a at 3 million units per day on days 30-58. These patients were treated on an institutional review board-approved protocol and gave signed informed consent. Plasma samples were obtained hourly for 6 hours after the morning ATRA dose on days 1, 29, and 57. ATRA levels were measured by a modification of previously published methods (6). Both patients had a large decline in peak ATRA concentrations after a month of treatment (Table 1).

Levels observed after daily dosing with IFN α-2a plus ATRA were slightly higher than those seen with daily ATRA alone, but they did not approach the initial peak ATRA concentrations.

An earlier report (7) on three patients also demonstrated that continuous IFN α-2a therapy did not usually maintain high ATRA plasma levels when it was added to continuous ATRA therapy. There are many mechanisms by which a combination of ATRA and IFN α-2a might be more active than either agent used alone; these mechanisms include increased sensitivity to IFN α-2a produced by retinoid-associated increases in IFN α-2a-stimulated transcription or IFN α-2a induction of RAR α, which might augment transcription of RAR-regulated genes (8-10).

Combinations of retinoids and interferon are a promising area for further investigation and have been active in the treatment of a number of tumor types that would not necessarily have been expected to respond to either agent alone (11,12). The regimen described by Toma et al. (3) may reduce toxicity compared with the result achieved with simultaneous therapy with IFN α-2a and ATRA. However, its activity is unlikely to be related to effects of IFN α-2a on plasma retinoid levels.

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References

(3) Toma S, Palumbo R, Giordano D, Arcuri T, Regazzi MB. Response of aleukemic granu-

Table 1. All-trans-retinoic acid (ATRA) levels*

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Day</th>
<th>Therapy</th>
<th>Peak concentration, mg/L</th>
<th>AUC, mg/L × h</th>
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<tr>
<td>1</td>
<td>1</td>
<td>ATRA</td>
<td>0.264</td>
<td>0.66</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>ATRA</td>
<td>0.019</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>29</td>
<td>ATRA</td>
<td>0.03</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>57</td>
<td>ATRA plus IFN α-2a</td>
<td>0.03</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>ATRA</td>
<td>0.856</td>
<td>2.26</td>
</tr>
<tr>
<td></td>
<td>29</td>
<td>ATRA</td>
<td>0.037</td>
<td>0.1</td>
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<tr>
<td></td>
<td>57</td>
<td>ATRA plus IFN α-2a</td>
<td>0.101</td>
<td>0.21</td>
</tr>
</tbody>
</table>

*AUC = area under the curve; IFN α-2a = interferon alfa-2a.
A Rare Case of Prednimustine-Induced Myoclonus

Prednimustine is frequently used in the treatment of chronic lymphocytic leukemia, non-Hodgkin’s lymphoma, Hodgkin’s disease, and ovarian and breast cancers. However, care should be taken to recognize early neurologic side effects that may have disabling consequences.

We report here a rare neurologic side effect associated with administration of prednimustine. A 79-year-old woman presented with weight loss, night sweats, asthenia, bilateral inguinal lymphadenopathy, and splenomegaly. She had had a 19-year history of low-grade follicular lymphoma, which had been treated 8 years previously by various chemotherapy regimens, including prednimustine.

A biopsy of an inguinal adenopathy disclosed Hodgkin’s disease, histologically different from the previously known lymphoma. She was treated with an oral combination of lomustine at a dose of 80 mg/m² on day 1 and etoposide at a dose of 100 mg/m² and prednimustine at a dose of 60 mg/m², both given on days 1 to 5 (corresponding to a total dose of chlorambucil of 6 mg/kg), and she was premedicated with allopurinol and ondansetron. On day 3, she noticed abnormal jerks of her hands, which increased during the subsequent days and finally involved the four limbs. On day 6, unable to stand, she fell and broke her right arm. Neurologic assessment at the emergency room disclosed severe myoclonia of the four limbs. Her mental state and conscious state were normal, and laboratory tests showed no electrolyte abnormalities. Clonazepam was introduced, and the myoclonia gradually decreased and disappeared on day 8. A medical history revealed that the patient had experienced the same hand jerks 8 years before while taking prednimustine. We replaced prednimustine with prednisone in subsequent treatment cycles, and the myoclonus did not reappear.

Prednimustine is an ester of prednisolone and chlorambucil. Elimination of chlorambucil and its metabolite phenylacetic mustard is prolonged after oral administration of prednimustine compared with chlorambucil alone. Neurotoxicity was dose limiting in a phase I trial of high-dose chlorambucil (1), and chlorambucil-related myoclonus has been described (2) in a 71-year-old woman treated for a lymphocytic lymphoma with a 5-day regimen of chlorambucil and dexamethasone. In this patient, the jerks appeared on day 3, culminated on day 7, and disappeared gradually after another week.

Three cases of prednimustine-induced myoclonus have also been reported (3) in women previously treated with cisplatin for an ovarian cancer. The myoclonia developed on day 4 during a 5-day regimen of prednimustine (120 mg/m² per day) and disappeared after cessation of the chemotherapy and administration of diazepam. Hypomagnesemia found in these three patients was considered a possible contributing factor.

The mechanism of chlorambucil-induced myoclonus is not known. Myoclonus arises from the central nervous system in a complex interaction between brain stem, cortex, and cerebellum. It is found in several neurologic diseases, including mitochondrial myopathies with central nervous system dysfunction, in which deficiencies of components of the respiratory chain are observed (4). Similarly, the neurotoxicity of an alkylating agent (5) is due to the interference with oxidative phosphorylation in the mitochondria by their metabolites.

References

(5) Kupfer A, Aeschlimann C, Wermuth B, Cerny acetic mustard is prolonged after oral administration of prednimustine compared with chlorambucil alone. Neurotoxicity was dose limiting in a phase I trial of high-dose chlorambucil (1), and chlorambucil-related myoclonus has been described (2) in a 71-year-old woman treated for a lymphocytic lymphoma with a 5-day regimen of chlorambucil and dexamethasone. In this patient, the jerks appeared on day 3, culminated on day 7, and disappeared gradually after another week.

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