Clinical Availability of ATRA for Patients With Suspected Acute Promyelocytic Leukemia: Why Guidelines May Not Be Followed

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ABSTRACT

Background: All-trans retinoic acid (ATRA) serves as the backbone of the management of patients with acute promyelocytic leukemia (APL), with guidelines recommending the initiation of ATRA as soon as APL is suspected. As a regional referral center for patients with acute leukemia, those who are suspected of having APL are often transferred to our facility. However, many referring centers are unable to initiate treatment using ATRA. We conducted an exploratory analysis of the clinical availability of ATRA and the factors limiting access to this critical drug. Patients and Methods: The United States was divided into 6 geographic regions: Northwest, Southwest, Central, Southeast, Northeast, and the Great Lakes. Twenty hospitals were randomly selected from states within each of these regions and were surveyed as to whether they typically treated patients with acute leukemia, and reported reasons for not stocking ATRA (if not available). Results: Less than one-third of hospitals queried (31%) had ATRA in stock. Neither the size of the hospital nor the hospital’s status as academic versus nonacademic (53% vs 31%; P = .08) influenced ATRA availability. Of the hospitals that referred patients with APL, only 14% (7/49) had ATRA readily available. Hospitals that treated patients with APL were more likely to have ATRA available than referring centers (58% vs 14%; P = .000002). Conclusions: Nearly two-thirds of the hospitals surveyed that cared for patients with acute leukemia do not have ATRA immediately available. Moreover, the vast majority of hospitals that refer patients to other centers do not have ATRA. These findings should spur investigation into the impact of immediate ATRA availability on the morbidity and mortality of patients with APL. A call by hematologists nationwide to their formulary committees is warranted to ensure that this lifesaving medication is available to patients suspected of having APL.

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Background

Acute promyelocytic leukemia (APL) is recognized as a true hematologic emergency, and all-trans retinoic acid (ATRA; tretinoin, Teva Pharmaceutical Industries Ltd) serves as a uniform backbone of the early care and management of patients with APL.1 SEER-17 data from 2001 to 2007 showed that APL represented 7.4% of all patients diagnosed with acute myeloid leukemia (AML), with an incidence rate of 2.7%.2 Although the 5-year survival is higher in APL than in other AML subtypes, the 30-day mortality for APL is noteworthy, ranging from 15% to 25%.3 Proposed reasons for early mortality in APL include disease-related complications such as disseminated intravascular coagulopathy (DIC; bleeding, intracranial hemorrhage), treatment-related complications, and a lack of timely initiation of treatment.2,4 Although ATRA was first investigated as a salvage therapy for patients with relapsed or refractory disease, current European LeukemiaNet guidelines5 and NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for AML6 call for the early use of ATRA in patients suspected of having APL, even before genetic confirmation of the disease. Furthermore, because ATRA can significantly mitigate DIC, known to be one of the early complications of APL, the NCCN and European LeukemiaNet guidelines support the prescription of ATRA as soon as there is clinical suspicion of the diagnosis.5,6

As a regional referral center for the care of patients with advanced myeloid malignancies, our facility receives numerous requests for the transfer of care of patients suspected of having APL. Consider the case of a female patient aged 63 years who initially presented to her primary care provider after experiencing a week of fatigue and easy bruising. She was referred to the nearest community emergency room for further evaluation when initial laboratory work revealed a new pancytopenia accompanied by profound thrombocytopenia. Upon hematopathologist review of a bone marrow aspirate, she was found to have features consistent with APL. The patient was given appropriate supportive care with transfusion of blood products, and our facility was contacted with a request for transfer.
Given the concern for APL, immediate initiation of ATRA was recommended before transfer. Unfortunately, due to limited bed availability, transfer was delayed several days. In the interim, her condition continued to deteriorate, requiring ICU admission for DIC and thus dramatically increasing the risk of poor outcomes during transfer. Upon the patient’s eventual transfer, a review of records revealed that ATRA had never been started.

Unfortunately, the circumstances surrounding this patient are not unique. The primary outcome of this study was to determine the clinical availability of ATRA for patients with a suspected diagnosis of APL at regional medical centers throughout the United States. The secondary objective was to identify the potential hurdles limiting the availability of ATRA at these institutions.

**Patients and Methods**

The United States was divided into 6 geographic regions: Northwest, Southwest, Central, Southeast, Northeast, and the Great Lakes. A state from each of these regions was randomly selected (Washington, Arizona, Missouri, Georgia, Massachusetts, and Michigan). Hospitals with a capacity of >100 beds were chosen from the American Hospital Directory (http://www.ahd.com/), and all hospitals were assigned a number. These numbers were entered into a random number generator, and the first 20 hospitals from each region (120 total) were selected for the survey (excluding repeats). Two hospitals were excluded because of a lack of response after repeated attempts. The following questions were asked of the hospital’s inpatient pharmacist:

1. Does your hospital treat acute leukemia or does it refer to other hospitals?
2. Do you have ATRA (oral), 10 mg tablets on the formulary or immediately available in stock as a nonformulary request?
3. If no, why not?

Statistical analyses were performed using SPSS Statistics, version 20.0 (IBM Corp.). Quantitative variables are reported as the number (percentage) and dichotomous variables were compared using the chi-square test. A value of $P<.05$ was considered significant.

**Results**

ATRA was available in less than one-third of the hospitals queried (31%; Table 1). There were no identifiable differences in the availability of ATRA based on hospital size (inpatient beds) or academic versus nonacademic status of the hospital (53% vs 35%; $P=.08$). In hospitals that referred to other institutions for the care of their patients with leukemia (49/118; 41.5%), only 14% ($n=7$) had ATRA on their formulary or available in stock as a nonformulary request that could act as a bridge before patient transfer. There was a significant difference in hospitals that had ATRA available based on whether they were a leukemia treatment center versus a referring center (40/69 [58%] vs 7/49 [14%], respectively; $P=.000002$). Alarming, even for hospitals stating that they treated patients with acute leukemia, 42% did not have ATRA immediately available in stock for patients.

The survey identified 3 common barriers to the availability of ATRA in hospitals: (1) the drug had not been recently requested by a physician and therefore was not available, (2) the inpatient pharmacist was not familiar with the drug, and (3) the hospital relied on associated hospitals or cancer centers to provide the drug to the patient.

**Discussion**

APL is an aggressive subtype of AML characterized by a distinct morphology, cytogenetic chromosomal translocation, clinical presentation, and therapeutic recommendation.1,5,6 Although APL is known to be the most curable form of acute leukemia, a high proportion of patients presents with or are at high risk of hemorrhagic and thrombotic complications. As a result, a high early death rate can occur.3 The first 24 hours are crucial in diagnosing and instituting treatment with ATRA to reverse DIC, a life-threatening coagulopathy. ATRA can significantly mitigate DIC, and immediate initiation of ATRA therapy and supportive measures aimed at counteracting disease-associated coagulopathy improve early survival.7 Delaying ATRA administration seems to contribute to increased hemorrhagic complications and an early death rate.4,7 In one report, the incidence of early death in 204 patients with APL was 11%, with most deaths resulting from hemorrhage (61%).7 High-risk patients with APL (defined as WBC count >10,000/µL) who received ATRA had a lower overall early death rate.7 When ATRA was administered within 24 hours of suspicion of APL, the rate of early death due to hemorrhage was 33%. However, when ATRA was administered >24 hours after the initial

<p>| Table 1. Immediate Availability of ATRA by Region |</p>
<table>
<thead>
<tr>
<th>Region</th>
<th>State</th>
<th>Hospitals With ATRA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northeast</td>
<td>Washington</td>
<td>13/20 (65)</td>
</tr>
<tr>
<td>Southwest</td>
<td>Arizona</td>
<td>9/20 (45)</td>
</tr>
<tr>
<td>Central</td>
<td>Missouri</td>
<td>4/20 (20)</td>
</tr>
<tr>
<td>Great Lakes</td>
<td>Michigan</td>
<td>11/19 (58)</td>
</tr>
<tr>
<td>Southeast</td>
<td>Georgia</td>
<td>7/20 (35)</td>
</tr>
<tr>
<td>Northeast</td>
<td>Massachusetts</td>
<td>4/19 (21)</td>
</tr>
<tr>
<td>All regions</td>
<td>All states</td>
<td>37/118 (31)</td>
</tr>
</tbody>
</table>

Abbreviation: ATRA, all-trans retinoic acid.
Clinical Availability of ATRA

This study represents a verbal reporting of accessibility to ATRA based on a telephone survey. We attempted to reach individuals knowledgeable about the formulary at each institution, and therefore focused our discussions primarily with an inpatient pharmacist at each institution. However, as noted in the “Results” section, one reason for the lack of availability of ATRA was a lack of familiarity with the product, which could lead to inaccuracies originating from the reporting practitioner about whether the medication was truly available at the hospitals. Although most institutions require 24 to 48 hours to make medical requests for and to acquire nonformulary medications, we did not specifically inquire as to the time frame for procuring ATRA at centers reporting the medication as nonformulary. Our results are similar to findings from a survey of the hospitals in Michigan and Louisiana that reportedly treat patients with APL, which found that 26% (6/23) of these hospitals had ATRA on formulary and that the most common reason for not having ATRA on formulary was that the pharmacist was unfamiliar with the drug.5

Conclusions
After surveying 120 randomly selected hospitals, our study suggests that ATRA may not be available at many hospitals across the United States and that this may be a substantially larger issue at referring hospitals. Hospitals in the central and southeastern United States were the least likely to have ATRA available. Our findings should spur an investigation into the impact of early access to ATRA on morbidity and mortality in APL. Furthermore, a call from hematologists nationwide to their formulary committees is warranted to ensure that this lifesaving medication is available to patients in a timely manner.

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References