Original Study

Pseudotumor Cerebri in Acute Promyelocytic Leukemia Patients on Intergroup Protocol 0129: Clinical Description and Recommendations for New Diagnostic Criteria

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Abstract

Pseudotumor cerebri (PTC) is a rare side effect of all-*trans* retinoic acid (ATRA). We examined patients with acute promyelocytic leukemia (APL) treated on I0129 who developed PTC. This trial evaluated the role of ATRA alone during induction and/or as maintenance therapy. We found that 1.7% of patients receiving ATRA developed "probable" PTC. We review the literature on PTC in APL and discuss diagnostic criteria.

Background: Multiple randomized trials have demonstrated a benefit for all-*trans* retinoic acid (ATRA) in patients with acute promyelocytic leukemia (APL). Pseudotumor cerebri (PTC) is an infrequently reported adverse effect of ATRA. **Methods:** We examined the incidence, clinical course, and outcomes of patients with APL treated on Intergroup Protocol 0129 (I0129) who developed PTC. This trial evaluated the role of ATRA alone during induction and/or as maintenance therapy. **Results:** Of the patients on trial, 240 received ATRA during induction, maintenance, or both; 8 had a clinical suspicion for PTC. Upon review of individual cases, this was felt to be "probable" in 4 patients, "possible" in 1 and "unlikely" in 3 due to lack of diagnostic criteria or presence of a more likely alternate diagnosis. **Conclusions:** "Probable" PTC occurred in 1.7% of patients who received ATRA during induction and/or maintenance therapy. In agreement with previous reports, the incidence of PTC in APL patients receiving ATRA was higher in the pediatric population. Here, we discuss the method for diagnosing PTC in the setting of ATRA therapy and management strategies.

Clinical Lymphoma, Myeloma & Leukemia, Vol. ■, No. ■, ■-■
Keywords: Acute promyelocytic leukemia, All-*trans* retinoic acid, ATRA, Neurotoxicity, Pseudotumor cerebri

Introduction

Multiple randomized trials have demonstrated that all-*trans* retinoic acid (ATRA) significantly improves the outcome of patients with acute promyelocytic leukemia (APL).[1,2] While ATRA is usually well-tolerated, multiple side effects may occur, including neurologic toxicities such as headache and more rarely, pseudotumor cerebri syndrome (PTC). The mechanism of ATRA neurotoxicity may be similar to vitamin A toxicity, which is a known cause of PTC, as high doses of ATRA can lead to retinoids enhancing the production of cerebrospinal fluid (CSF). In a study comparing CSF retinol levels in patients with idiopathic PTC to those without, a higher level of vitamin A was noted in the CSF of affected patients, none of whom had known vitamin A toxicity.[3] Additionally, ATRA may alter the lipid constituents of the arachnoid villi, which disturbs the normal transport system and therefore CSF cannot be absorbed.[4]

PTC may be a primary disorder, most commonly seen in obese female patients of childbearing age, or it may be secondary to other causes such as cerebral venous abnormalities, or associated with various medical conditions (such as Addison's Disease), or medications (such as ATRA therapy). In 2013, the diagnostic criteria for the syndrome were revised, with requirements for diagnosis

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Submitted: Oct 16, 2015; Revised: Nov 11, 2015; Accepted: Nov 17, 2015

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2152-2650/$ - see frontmatter
http://dx.doi.org/10.1016/j.clml.2015.11.018

including papilledema, normal neurologic exam except for cranial nerve abnormalities, normal neuroimaging without evidence of hydrocephalus, mass, or structural lesion, and no abnormal meningeal enhancement on magnetic resonance imaging (MRI) or contrast-enhanced computed tomography (CT), normal CSF composition, and elevated lumbar puncture (LP) opening pressure ($\geq$ 250 mm Hg or $\geq$ 280 mm Hg for non-obese children). Further, the diagnosis may be made in the absence of papilledema if all of the above criteria are satisfied and the patient has unilateral or bilateral abducens nerve palsy. If there is neither papilledema nor a sixth cranial nerve palsy, the diagnosis can be suggested, but not confirmed with additional neuroimaging characteristics.[5] While headache is the most common presenting symptom of PTC,[6] presence of headache is not part of the 2013 diagnostic criteria.

PTC has frequently been described in the literature as an adverse effect of ATRA therapy, usually in single case reports,[4,7-29] making an estimation of its true incidence difficult. Here, we discuss the series of patients on clinical trial I0129 in which there was a clinical suspicion for PTC, focusing on diagnostic criteria in this select population, and how to treat such patients.

Methods

Treatment With ATRA

Intergroup 0129 was a prospective trial conducted between April 1992 and February 1995 in which patients with newly diagnosed APL by morphology were randomized to receive either ATRA 45 mg/m^2/day divided into 2 daily doses or to daunorubicin 45 mg/m^2 (1.5 mg/kg for children $<$ 3 years of age) by intravenous (IV) bolus on days 1 to 3 and cytosine arabinoside 100 mg/m^2 (3.3 mg/kg for children $<$ 3 years of age) by continuous IV infusion on days 1 to 7 for induction. Patients on the ATRA induction arm were required to have white blood cells (WBCs) $\leq$ 10,000/μL at presentation, or after hydroxyurea, prior to initiating ATRA. Patients who failed to respond to ATRA for induction after a maximum of 90 days, or failed before 90 days of ATRA because of toxicity or progressive disease, were permitted to cross over to the chemotherapy arm. Patients randomized to induction chemotherapy who did not achieve complete remission (CR) after 2 cycles did not cross over to the ATRA arm but were removed from the study and treated at the physician's discretion. For consolidation, patients who had a CR with chemotherapy or ATRA received 2 cycles of consolidation therapy.[2]

For maintenance, patients in CR after both cycles of consolidation chemotherapy were randomly assigned to either 45 mg of ATRA per square meter per day given orally in divided doses every 12 hours for 1 year or to observation.[2]

Patients

A total of 397 patients were assessed for eligibility; 18 were excluded, leaving 379 patients for induction randomization. For induction therapy, 191 were randomized to receive chemotherapy and 188 were randomized to receive ATRA. Of the 191 patients randomized to chemotherapy for induction, 129 achieved a complete remission with 105 randomized for maintenance (52 randomized to ATRA maintenance and 53 randomized to observation). Of the 188 patients randomized to ATRA induction, 142 obtained a complete remission with 113 randomized for maintenance (49 randomized to ATRA maintenance and 64 randomized to observation). In total, 240 patients were evaluable for analysis on the ATRA arms (induction, maintenance, or both; Figure 1).[30] Details of patient characteristics and outcomes have previously been reported.[2]

Diagnosis

The diagnosis of PTC was made in the presence of signs and symptoms of intracranial hypertension without clinical or radiological evidence of infective or space occupying lesions. "Definite" PTC met all of the 2013 diagnostic criteria: (1) presence of papilledema, (2) normal neurologic exam except for cranial nerve abnormalities, (3) normal neuroimaging without evidence of hydrocephalus, mass, or structural lesion, and no abnormal meningeal enhancement on MRI or contrast-enhanced CT, and (4) normal CSF composition with elevated LP opening pressure. Because of the clinical circumstances associated with APL and the frequent inability to perform a LP safely in some of these patients, we constructed additional criteria to address the patients in this cohort so we could delineate those in whom PTC was probable even though they did not meet the full 2013 diagnostic criteria. Neurological exams and CSF composition were assumed to be normal unless explicitly stated otherwise, and in cases where the opening pressure was not available from the LP, it is assumed that pressure was elevated to such a degree to meet diagnostic criteria. Thus, patients with "probable" PTC met all but one of the diagnostic criteria. "Possible" cases were missing two of the criteria, and "unlikely" cases were those in which an alternate diagnosis was more likely than PTC or when only 0 to 1 criteria were present (Table 1).

Treatment of Pseudotumor Cerebri

Treatment of PTC, when suspected, was variable. In some instances, patients were provided with symptomatic therapy such as dexamethasone and narcotics, and in other cases, the ATRA was held and restarted either at the same dose or a lower dose. Data were not available regarding response to specific interventions within this series.

Results

Clinical Characteristics of Patients With Pseudotumor Cerebri

Probable Cases. Case 1

During induction, an 8-year-old girl developed a grade 2 headache on day 4 of ATRA therapy. The headache persisted until day 20 when a head CT scan was performed, which was normal. An ophthalmologist saw the patient, and bilateral papilledema was noted on funduscopic exam. For treatment of presumed PTC, this patient was given dexamethasone. This patient meets all criteria for PTC except an LP was not performed, making the diagnosis "probable."

Case 2

During induction, a 19-year-old boy developed a headache on day 9 of ATRA therapy. He underwent an LP for workup, which showed an elevated CSF pressure of 420 mm water. Papilledema was noted in the temporal region of his optic discs. ATRA was held, but resumed on day 12. Neuroimaging was not documented, though this patient met all other criteria for PTC, making this case "probable."

Case 3

During induction, an 11-year-old boy developed diplopia with papilledema on day 13 of ATRA therapy, with a sixth nerve palsy on day 14 of therapy. Head CT scan was negative on day 14. The