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Case report

# High pseudotumor cerebri incidence in tretinoin and arsenic treated acute promyelocytic leukemia and the role of topiramate after acetazolamide failure

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ABSTRACT

Dual differentiation therapy with arsenic trioxide and tretinoin (all-*trans*-retinoic acid; ATRA) for the management of low and intermediate risk acute promyelocytic leukemia has recently been recommended by the National Comprehensive Cancer Network. Some less common toxicities of the combination may have yet to be fully realized. Of ten patients we have treated thus far, five (50%) have developed pseudotumor cerebri. In one patient, temporary discontinuation of ATRA and initiation of acetazolamide controlled symptoms. In four patients, topiramate was substituted for acetazolamide to relieve symptoms and allow ATRA dose re-escalation. We conclude that providers should monitor for pseudotumor cerebri and consider topiramate if acetazolamide fails.

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## 1. Introduction

Acute promyelocytic leukemia (APL) is an aggressive myeloid malignancy defined by the presence of the PML-RARα fusion gene produced by a translocation between chromosomes 15 and 17. Through risk stratification and incorporation of tretinoin (all-*trans*-retinoic acid; ATRA) into treatment, patient outcomes have drastically improved with complete response (CR) rates reaching $>90\%$ when combined with chemotherapy [1–3]. Most recently, dual differentiation therapy with ATRA and arsenic trioxide (ATO) (Table 1), has become a recommended first-line regimen by the National Comprehensive Cancer Network for the management of patients with low/intermediate risk APL (white blood cell (WBC) count $<10\times10^9$/L), or patients with high risk disease who are unable to receive anthracycline-based chemotherapy [4]. ATO binds to the PML end of the fusion protein resulting in apoptosis of APL cells [5]. A randomized controlled trial by Lo-Coco et al. [6] demonstrated complete remission rates of 100% with dual differentiation therapy, proving non-inferiority of the ATO-ATRA combination over ATRA plus chemotherapy in the management of low/intermediate risk APL.

Pseudotumor cerebri (PTC), also known as idiopathic intracranial hypertension, is a condition characterized by an increase in intracranial pressure, without cerebrospinal fluid (CSF) abnormalities or radiological evidence of other intracranial pathology (hydrocephalus, mass, structural or vascular lesion) [7]. PTC following ATRA administration for APL has been well described [8–26]. However, reports of PTC resulting specifically from dual differentiation therapy are currently lacking, and there is a paucity of evidence describing management of this condition specifically in patients with APL, where continuation of therapy is necessary for optimal clinical outcomes.

Although the exact mechanism of ATRA induced PTC is currently unknown, a variety of medications are used in its management including carbonic anhydrase inhibitors, diuretics, corticosteroids, and analgesics. Acetazolamide, a carbonic anhydrase inhibitor, is the most commonly used agent in the management of non-drug induced PTC and is thought to work through reduction of CSF production. More recently, the anticonvulsant topiramate has been viewed as an attractive treatment option for idiopathic PTC given its activity as a carbonic anhydrase inhibitor (mostly at receptor subtypes II and IV) and its efficacy as a migrainolytic [27–29]. The precise mechanism of both migrainolysis and anti-epileptic efficacy is unknown, however the drug is known to antagonize sodium channels, augment the effect of gamma-aminobutyrate (GABA) at receptor subtype A, and antagonize the AMPA/kainate subtypes of the glutamate receptors [30].

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**Table 1**
Schedule of induction and consolidation components of ATO–ATRA dual differentiation regimen [6,32].

| | | |
|---|---|---|
| **Induction**[a] | | |
| ATRA[b] | AND | ATO[b] |
| 45 mg/m$^2$/day divided twice daily in equal doses | | 0.15 mg/kg/day in 500 mL normal saline intravenous over two hours |
| Bone marrow biopsy on day 28: If $<5\%$ blasts and no abnormal promyelocytes, discontinue ATRA and ATO until occurrence of CR[c]. Biopsy repeated weekly until criteria for drug discontinuation met. | | |
| **Consolidation** | | |
| ATRA[b] | AND | ATO[b] |
| 45 mg/m$^2$/day divided twice daily in equal doses for two weeks every 4 weeks for a total of 7 cycles | | 0.15 mg/kg/day in 500 mL normal saline intravenous over two hours 5 days a week for 4 weeks every 8 weeks for a total of 4 cycles |

[a] On days 1–5 of induction therapy, all patients received therapy with methylprednisolone 48 mg PO daily for differentiation syndrome prophylaxis.
[b] ATRA, All-*trans* retinoic acid; ATO, arsenic trioxide.
[c] CR, complete response defined by neutrophil and platelet counts greater than $1 \times 10^9$/L and $100 \times 10^9$/L, respectively, together with the noted marrow findings.

**Table 2**
Disease characteristics of patients developing pseudotumor cerebri (PTC) on dual differentiation therapy.

| Case | At diagnosis of APL | | | | | At diagnosis of PTC | | PTC Symptom Onset |
|---|---|---|---|---|---|---|---|---|
| | Risk category[a] | WBC[b] (cells/L) | Plt[b] (cells/L) | PMC[b] (%) | PML-RAR-α FISH[b] (%+cells) | ICP[b] (cm $H_20$) | BMI[b] kg/m$^2$ | # of days after initiation of ATO–ATRA |
| **1** | Intermediate | $5 \times 10^9$ | $39 \times 10^9$ | 93 | 90 | 35 | 32.1 | Induction: day 1 |
| **2** | Low | $0.9 \times 10^9$ | $49 \times 10^9$ | 6 | 83 | 39 | 30.2 | Induction: day 1 |
| **3** | Low | $2.5 \times 10^9$ | $77 \times 10^9$ | 66 | 11 | 28 | 37.1 | Induction: day 1 |
| **4** | Low | $5.8 \times 10^9$ | $41 \times 10^9$ | 26 | 92 | 36 | 28.5 | Induction: day 31 |
| **5** | Intermediate | $3.4 \times 10^9$ | $29 \times 10^9$ | 44 | 85 | 27 | 23.6 | Consolidation[c]: Cycle 1, day 3<br>Cycle 2, day 3<br>Cycle 3, day 1 |

[a] "Low" risk defined platelet count $>40 \times 10^9$/L and white blood cell count $<10 \times 10^9$/L; "Intermediate" risk defined as platelet count $<40 \times 10^9$/L, and white blood cell count $<10 \times 10^9$/L.
[b] WBC, white blood cell count; Plt, platelet count; PMC, promyelocytes; FISH, fluorescence *in-situ* hybridization; ICP, intracranial pressure; and BMI, body mass index.
[c] A "cycle" of consolidation refers to the eight week cycles of arsenic trioxide therapy (total of four cycles).

From November 2012, through January 2014, ten patients with low or intermediate risk APL received upfront dual differentiation therapy with the ATO–ATRA combination [4]. Out of these ten patients, we describe five (50%) cases of PTC which occurred following the initiation of dual differentiation therapy and their clinical courses, with an emphasis on our experience with the substitution of topiramate in place of acetazolamide in non-responders.

## 2. Case 1

A 54 year old African American male was transferred to RPCI where workup revealed a diagnosis of APL (Table 2) and dual differentiation therapy was subsequently initiated (Table 1). That same evening, he complained of severe headache that was out of the ordinary for him with no other symptoms. Of note, he was also receiving concomitant diltiazem CD 180 mg daily, a medication known to inhibit CYP3A4 [31]. A head CT scan was without any abnormalities, and a lumbar puncture (LP) revealed an elevated intracranial pressure (ICP) of 35 cm $H_20$. ATRA was interrupted, and acetazolamide was started at 250 mg orally twice daily. After two days, his headache resolved and ATRA was restarted with an 80% dosage reduction. Headaches resumed upon ATRA reintroduction. However, therapy was continued, and acetazolamide was increased to 500 mg orally twice daily.

Acetazolamide was unable to relieve the headaches and was discontinued. Topiramate was initiated, with subsequent headache relief noted at a dose of 100 mg orally twice daily. With this therapy, ATRA was able to be re-titrated to a maximum of 40 mg orally twice daily (80% of initial dose) over two weeks until PTC recurred. Following therapeutic lumbar puncture, ATRA was resumed at 30 mg orally twice daily. A topiramate dose of 150 mg orally twice daily was needed to control symptoms for the remainder of induction. At no point during treatment was ATO interrupted. Upon discharge, the patient was prescribed topiramate 100 mg orally twice daily to begin the day prior to starting ATRA consolidation. He completed consolidation as planned. Four months following therapy completion, he remains in CR.

## 3. Case 2

A 24 year old Caucasian male with no past medical history was transferred to RPCI. Workup at revealed APL (Table 2) and ATO–ATRA induction was initiated (Table 1). The following day, the patient complained of headaches that had been occurring since his first dose of ATRA and were poorly controlled with opiates. Additionally, the patient was experiencing nausea, which was relieved with ondansetron. At that point, acetazolamide at a dose of 250 mg orally twice daily was added to be taken half an hour prior to ATRA dosing.

After three days, the patient experienced mild relief of headaches. Reduction of the ATRA dose by 50% further relieved his pain. However, he began feeling increasingly nauseous with vomiting episodes for twenty-four hours. A brain CT showed no abnormalities, and an LP was diagnostic for PTC with an ICP of 39 cm $H_20$. ATRA was held for three doses and acetazolamide continued. Once reinitiated, ATRA was titrated up to 30 mg orally twice daily over five days with acetazolamide also increased to 500 mg orally twice daily. Despite acetazolamide, he began to complain of headaches again and was subsequently changed from acetazolamide to topiramate 100 mg orally twice daily. ATRA was then titrated over three days up to full dose (50 mg orally in the morning and 60 mg

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