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Arsenic trioxide for acute promyelocytic leukemia in a patient on chronic hemodialysis

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ABSTRACT

Acute promyelocytic leukemia (APL) is a rare acute leukemia generally considered curable with all-trans retinoic acid (ATRA) and arsenic trioxide (ATO). Some patients have co-morbidities that may limit the use of these agents and therefore impact curability. Adverse effects of ATO include life-threatening electrocardiographic abnormalities. ATO and its metabolites are partially excreted in the urine, and it is unclear to what extent ATO pharmacokinetics are impacted by hemodialysis. We present a patient on chronic hemodialysis successfully treated with ATO and ATRA for newly diagnosed APL. Complete molecular remission was achieved after induction and several drug-related toxicities were managed.

1. Background

Acute promyelocytic leukemia (APL) is a subtype of acute myeloid leukemia (AML) that is characterized by a translocation between chromosomes 15 and 17 [t(15;17)(q22;q21)] resulting in the fusion of the *PML* gene and the retinoic acid receptor alpha gene, *RARα* [1]. The PML/RARa fusion protein deregulates transcriptional control and disrupts PML nuclear bodies leading to a block in differentiation [2]. The incidence of APL is estimated to be 5 – 8% of AML cases, or about 1000 – 1500 patients annually in the U.S [3,4]. Patients with APL classically present with leukopenia and clinically evident disseminated intravascular coagulopathy and their upfront mortality is usually determined by fatal bleeding events. Importantly, patients who avoid bleeding complications and are able to receive therapy have greater than 90% chance of achieving molecular remission with most achieving long-term survival [5].

Current treatments for APL are centered on the combination of all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) with or without chemotherapy (anthracyclines and cytarabine) or the antibody-drug conjugate, gemtuzumab ozogamicin, based on the patient's condition and risk stratification [6]. Low-risk APL, classified by a white blood cell (WBC) count less than 10×10^9/L on presentation, is almost universally treated with the ATRA/ATO combination while regimens for high-risk presentations include an anthracycline or gemtuzumab ozogamicin to more rapidly control the high WBC count [6].

The most serious complications of the ATRA/ATO regimen are differentiation syndrome (DS) and electrocardiographic (ECG) abnormalities including QRS complex widening, ST segment depression, and QTc interval prolongation which may trigger torsades de pointes, a life threatening polymorphic ventricular tachycardia [7–9]. QTc prolongation may occur in 40% of patients receiving standard dosing of ATO [10]. Most of the ECG complications are attributed to ATO and in order to ensure safe administration, it is imperative to monitor the ECG and serum electrolytes regularly, and to minimize the use of other medications that may cause QTc prolongation [6].

ATO undergoes methylation by the liver, with a portion of metabolites excreted in the urine. Pharmacokinetic evidence indicates that patients with severe renal impairment have higher exposure to the primary active metabolite of ATO [10]. There is limited published experience in the use of ATO in patients with end stage renal disease (ESRD) on chronic hemodialysis (HD), which makes the use of ATO in this population challenging. We report a case of newly diagnosed low-risk APL in a patient with ESRD on chronic HD successfully and safely treated with ATO and ATRA.

2. Patient case

A 65-year-old male with a history of ESRD, hypertension, and a prior repair of thoracoabdominal aortic aneurysm was initially admitted to the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

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(Sibley Memorial Hospital, Washington, DC) for fever and headache. The ESRD was managed with intermittent HD three times weekly for several years. During the hospital course, he had radiographic evidence of pneumonia and methicillin-susceptible *Staphylococcus aureus* bacteremia. At the time, he was also pancytopenic with an initial complete blood count (CBC) revealing a WBC count of 1.38×10^9/L; hemoglobin (Hgb) 11.4 g/dL; and platelet count 46×10^9/L, all thought to be related to his ESRD and infection. However, his blood counts did not improve despite treatment of his infections with broad spectrum antibiotics and a bone marrow biopsy and aspirate were performed to assess the persistent pancytopenia. The aspirate smear revealed a myeloid maturation arrest with a marked increase in atypical promyelocyte blasts with rare cells revealing abundant Auer rods (Fig. 1). Flow cytometry indicated 73% phenotypically abnormal blasts that were negative for CD34 and HLA-DR and positive for CD13, bright CD33, and CD117. Fluorescence in situ hybridization (FISH) for t(15;17) was positive with 94% of nuclei containing the translocation which was confirmed by karyotype and molecular studies noting the fusion of *PML* and *RARα*.

A diagnosis of low-risk APL was made and following a discussion between the treating physician and the clinical pharmacist, the patient began induction therapy with ATRA 22.5 mg/m^2/dose PO twice daily plus ATO 0.15 mg/kg/dose (equivalent to 10 mg) IV daily, according to Lo-Coco et al. [11]. In addition, the patient received prednisone 0.5 mg/kg PO daily as prophylaxis for DS. ECGs were performed according to our institutional practice: prior to the first dose of ATO, twice weekly thereafter, and daily monitoring prior to each ATO dose if the QTc interval is greater than 500 ms (grade 3 or greater[12]). Hemodialysis continued on a thrice weekly schedule.

The patient tolerated the initial therapy well with emergence of a grade 1 peripheral neuropathy consisting of numbness and tingling in the bilateral toes by day 6 of the combination. No dose adjustments to the treatment regimen were made at that time and close clinical and laboratory monitoring was continued. On day 22 of therapy, a routine ECG revealed a QTc interval of 519 ms (grade 3) and ATO was held while the patient continued to receive ATRA. Daily ECGs remained > 500 ms until day 26 when the QTc was 492 ms (grade 2), and ATO was resumed every other day with daily ECG monitoring. The ATO was then re-escalated to daily dosing by day 29 with no further incidence of QTc prolongation greater than 500 ms for the remainder of the induction course (Fig. 2). The patient had evidence of hematologic recovery and was discharged on ATRA to follow-up in clinic. A bone marrow biopsy revealed normocellular marrow with trilineage hematopoiesis and no morphologic or immunophenotypic evidence of residual leukemia with a CBC confirming complete remission with WBC of 5.45×10^9/L; absolute neutrophil count (ANC) 4.51×10^9/L; Hgb 7.5 g/dL (untransfused); and platelet count 268×10^9/L. The bone marrow was negative for *PML-RARα* fusion by polymerase chain reaction, flow cytometry demonstrated no phenotypically abnormal cell population, and based on the consensus criteria [13], he was in a molecular complete remission and proceeded to consolidation therapy with ATRA and ATO.

The first cycle of consolidation was complicated by grade 1 maculopapular rash around day 11 which was consistent with dermatitis secondary to ATO. He was counseled to use supportive care agents for pruritus, including colloidal oatmeal wash and a low-potency non-prescription topical steroid. The QTc interval was once again prolonged at 505 ms (grade 3) on day 25 and ATO was held for the last two days of the cycle (Fig. 2). The patient continued on to ATRA only consolidation cycle 2 without further problems.

Consolidation cycle 3 day 8 was noteworthy as the patient presented to the outpatient clinic with significant fatigue, without dyspnea or chest discomfort. An ECG revealed a QTc interval of 493 ms (grade 2) and first-degree heart block with PR interval of 238 ms (grade 1), which resolved the following day (Fig. 2). The ATO was held until resolution of heart block and normalization of the QTc prolongation on day 11. ATO was held once more during this cycle for QTc prolongation on day 16. On day 22, the patient presented with sharp chest pain from the sternum around the right side to the back, and examination revealed a vesicular rash following the T3 dermatome, consistent with grade 2 herpes zoster infection. This was managed with oral valacyclovir and slowly resolved over the next several weeks. The remaining ATO doses in the cycle were

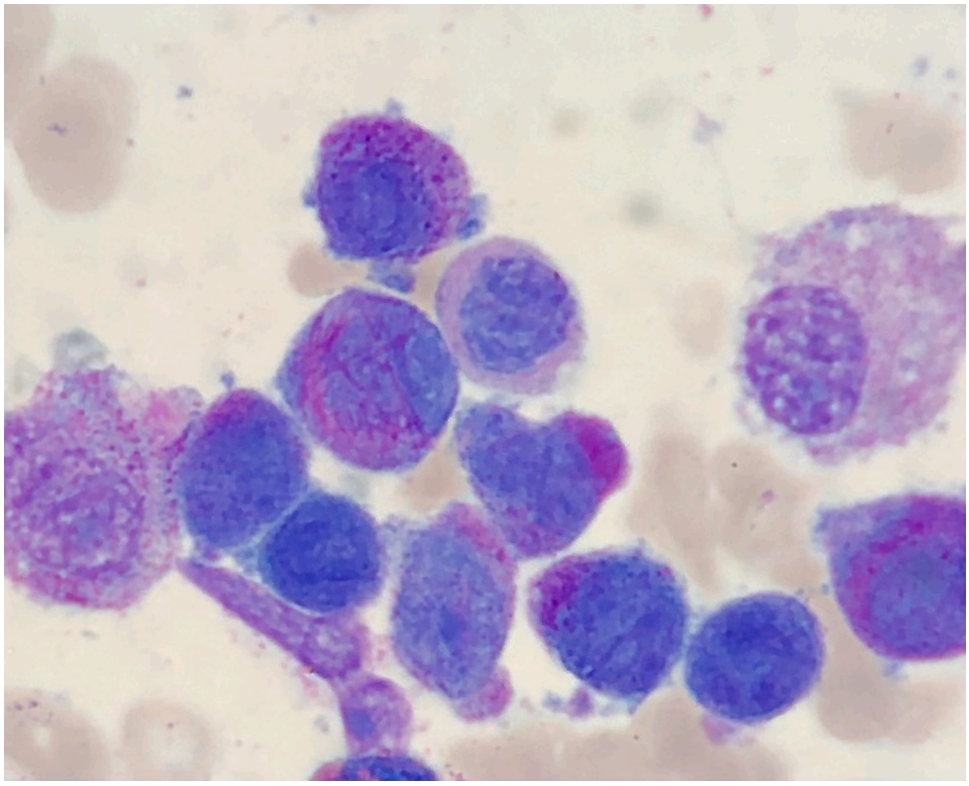

Fig. 1. Bone marrow aspirate with increased promyelocytes with numerous Auer rods.

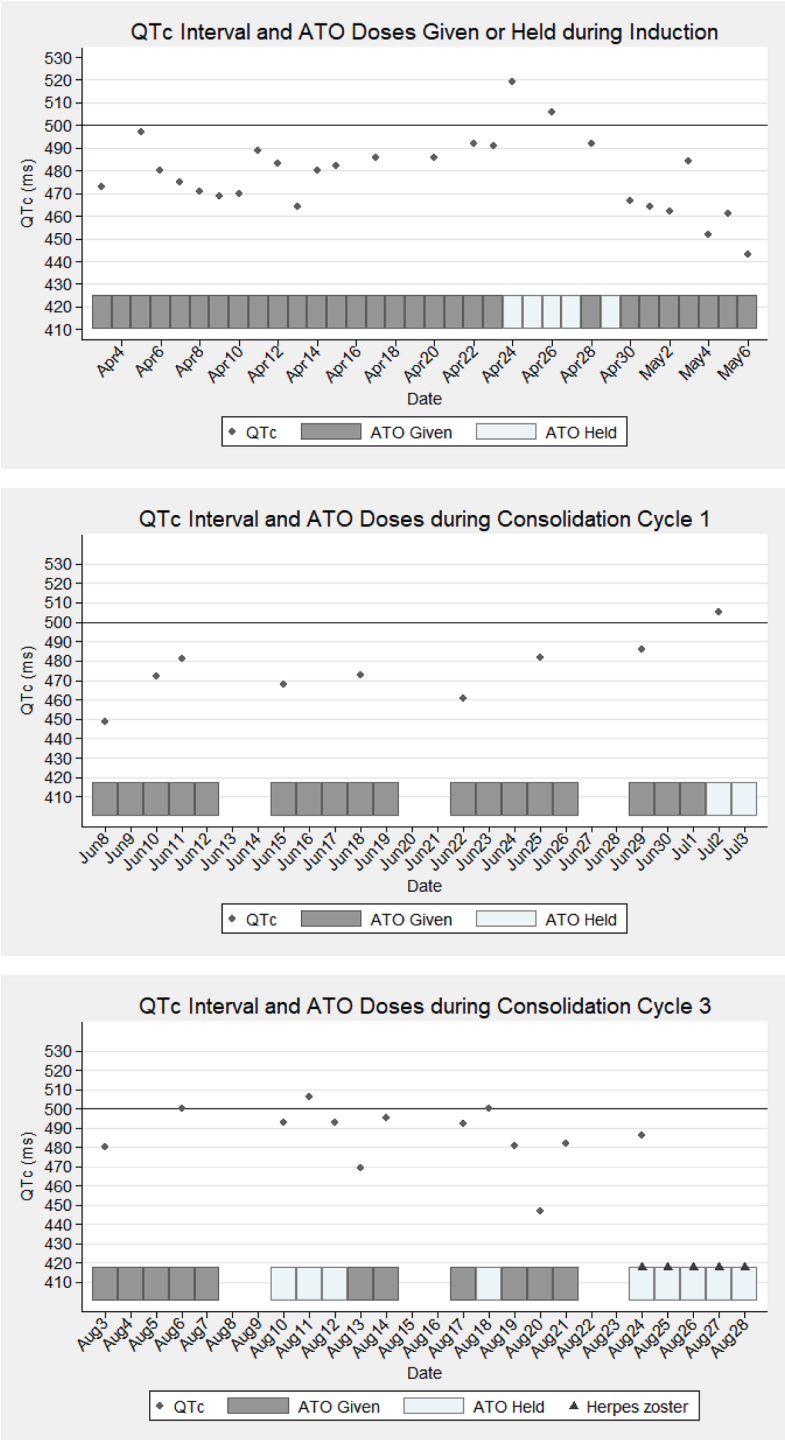

Fig. 2. Treatment course.

discontinued upon diagnosis of the infection with herpes zoster, with ATRA continuing as scheduled with cycle 4. The patient achieved and remains in complete hematologic and molecular remission.

3. Discussion

The ATRA/ATO regimen is considered curative for most patients diagnosed with low-risk APL. However, there are challenges in administering this combination to many patients due to toxicity or comorbid conditions. In this report, we present a case of a patient with ESRD on HD who was diagnosed with low-risk APL and treated with ATRA/ATO. The clinical course was complicated by several adverse effects that resulted in a total of 16 missed doses of ATO out of a planned 69 doses (23%) from induction through consolidation cycle 3. In each circumstance, the therapy was resumed with increased surveillance following holding the ATO. For example, during induction, the patient required a dose interruption and a reduction in dosing frequency for a grade 3 prolonged QTc interval. Upon return of the QTc interval to within normal limits, the daily dosing was resumed, resulting in a total of five doses of ATO held during induction. Grade 1 peripheral neuropathy occurred early in this cycle, which resolved quickly and did not require dose interruption or reduction.

The induction course foreshadowed the need for vigilant monitoring during consolidation with both QTc prolongation and first-degree heart block emerging, leading to six doses held between consolidation cycles 1 and 3. A further five doses of ATO were omitted in the final week of cycle 3 due to emergence of herpes zoster, of which an increased risk has been described in patients with APL receiving ATO [14]. Finally, grade 1 dermatitis was also thought to be secondary to ATO and was managed using supportive agents. Taken all together, our patient experienced common and rare adverse events associated with ATO including dermatitis (reported in 43% of patients), QTc prolongation (40%), peripheral neuropathy (<1%), and first-degree heart block (<1%) [10]. Each can pose a challenge to completing potentially curative therapy.

The cardiovascular effects and specifically the prolongation of the QTc interval are the most immediately life-threatening problems with ATO and were clinically prominent in our case. One challenge of QTc prolongation is the fact that it is commonly associated with many antineoplastic agents and supportive care treatments. Our patient was treated with several agents that may have contributed to the prolonged QTc interval including zolpidem, which was taken on most days during induction and presumably consolidation as well as ondansetron which was used during consolidation. To minimize dysrhythmias, our institutional practice includes nurse-managed protocols for repletion of potassium to a goal of 4 mmol/L and magnesium to a goal of 2.4 mg/dL. These protocols are required for patients receiving ATO and must be adjusted for patients with renal impairment or who are on renal replacement therapy. The patient's potassium and magnesium were within goal range throughout treatment and did not coincide with instances of QTc prolongation except on one day during consolidation, when electrolytes were below goal and repletion was administered.

There are not standardized practices to help teams balance the benefits of ATO in patients with APL on dialysis with the additional risks of QTc prolongation and safe electrolyte management. Part of the challenge has to do with determining safe and effective levels of ATO and the possibility of impaired clearance. Upon intravenous administration, ATO is immediately hydrolyzed to the primary active metabolite, arsenious acid, which is methylated by the liver and other organs to less active metabolites, monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA) [10]. While most of the drug is rapidly distributed to tissues, approximately 15% of the administered dose, plus the majority of MMA and DMA, are excreted in the urine. The pharmacokinetics of ATO, MMA and DMA have been evaluated in patients with advanced cancer and varying degrees of renal function. Patients with a creatinine clearance (CrCl) from 30 mL/min to > 80 mL/min had comparable AUC. However, patients with a CrCl < 30 mL/min had approximately 48% higher AUC for arsenious acid compared with patients with CrCl 〉 80 mL/min. The package labeling acknowledges a lack of pharmacokinetic information for patients on HD [10]. While arsenic concentrations were not measured in this case to direct ATO dosing or to allow comparison with other published cases, the patient's clinical outcome is telling.

To date, there are three published reports of ATO in patients receiving HD that are known to us. Emmons and colleagues report the use of ATO for relapsed APL in a patient on HD, with arsenic started at a dose of 0.1 mg/kg every other day [15]. With PCR positive for *PML-RARα* at day 60, the dosing was increased to 0.15 mg/kg every other day for 60 more days, after which remission was documented. Notably, ATRA was not included in the regimen due to severe hypertriglyceridemia and pancreatitis with prior administration. Firkin and colleagues titrated ATO dosing based on serum arsenic levels in four patients with renal failure, one of whom received HD, to approximate levels seen in patients with normal renal function receiving ATO 10 mg daily [16]. The patient on HD received ATO 10 mg three times per week after HD sessions, and was in molecular remission after 27 days of induction. Perreault and colleagues described an elderly patient with complicated course, who initially received only 11 doses of ATO over 7 weeks, with eventual increase to 10 mg three times per week given after HD with good response [17]. The patient had evidence of AV block on a pre-treatment ECG, and experienced first- and second-degree heart block during treatment with ATO.

Prescribing information for ATO includes guidance on dose modification for QTc prolongation, which broadly includes holding ATO until normalization of QTc, followed by resumption of ATO at 50% of the original dose, then increasing the dose step-wise over the course of 14 days [10]. With the known changes in pharmacokinetic parameters for patients with renal impairment, and lack of information for patients on HD, it is unknown if this dose modification strategy is ideal for the case presented here, however, it is acknowledged that this more conservative dosing may have reduced some of the adverse effects observed.

Our patient had evidence of hematologic recovery at day 33 of induction, and successfully attained hematologic and molecular CR at day 43 of induction within the expected time frame for the ATRA/ATO regimen with a reported median time to hematologic CR for patients who received ATRA/ATO was 32 days (range 22 – 68 days) [11].

4. Conclusion

This case report describes the use of ATO in combination with ATRA to treat low-risk APL in a patient with ESRD undergoing chronic HD, with CR achieved after induction. Previous case reports have described empiric dose reduction of ATO with or without subsequent dose escalation. We utilized full treatment dosing according to standard protocol with toxicities observed similar to those observed in patients with normal renal function. Diligent monitoring of ECGs and serum electrolytes, as well as proactive efforts to hold ATO dosing for grade 3 QTc prolongation were all vital to the success of this patient's treatment. We advocate that the availability of real-time pharmacokinetic studies may shed better light on the ideal dosing of ATO, and may allow for uninterrupted treatment for patients with renal dysfunction, ultimately optimizing safety and efficacy.

Declaration of Competing Interest

None

Acknowledgements

None

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