Severe Peripheral Neuropathy From Treatment With Arsenic Trioxide in a Patient Suffering From Acute Promyelocytic Leukemia

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Abstract

Treatment with arsenic trioxide (ATO) and all-trans retinoic acid (ATRA) is standard treatment for patients suffering from acute promyelocytic leukemia (APL). Peripheral neuropathy is a common sign of arsenic poisoning but reports of peripheral neuropathy from patients treated with ATO for APL are limited. We here present a case of a woman treated with standard regimes of ATRA-ATO for APL, who subsequently developed severe peripheral neuropathy from ATO poisoning.

Keywords: Arsenic trioxide; Leukemia; Acute promyelocytic leukemia; Peripheral neuropathy; Arsenic poisoning

Introduction

Acute promyelocytic leukemia (APL) is an extremely life-threatening neoplasm with severe coagulopathy at diagnosis, and is a distinct subtype of acute myeloid leukemia, characterized by the PML-RARA fusion gene generated from the reciprocal t(15;17)(q22;q21) chromosomal translocation. The disease is important to recognize, as patients rapidly deteriorate without proper treatment [1]. Since the advent of all-trans retinoic acid (ATRA) in combination with chemotherapy, and lately in combination with the inorganic arsenic compound, arsenic trioxide (ATO), the cure rate has increased tremendously. Today, ATRA in combination with ATO is standard treatment [1]. However, this so-called chemo-free treatment is not without side effect, i.e., ATO is a highly toxic chemical drug naturally present in various substances with a number of applications exploiting its toxicity [2].

Acute poisoning from inorganic arsenic in humans affects all organ systems. Symptoms include vomiting, profuse diarrhea, toxic cardiomyopathy, pulmonary edema, seizures and, ultimately, death. In the clinical setting, especially QTc-prolongation and hepatotoxicity must be addressed and carefully monitored during treatment with ATO [2, 3]. Lethal poisoning from inorganic arsenic, such as ATO, occurs at dosages from 1.0 to 3.0 mg/kg, if taken orally as a bolus. If exposed over a shorter period of time (14 days), the lethal dose is estimated to be about 0.6 mg/kg/day; whereas exposure > 365 days leads to fatal poisoning in dosages from 0.01 to 0.1 mg/kg/day [4].

Chronic, non-lethal levels of inorganic arsenic poisoning have different characteristics. Dermatological changes are seen in the form of hyperpigmentation, palmar and solar keratosis and Mees’ lines on finger and toe nails. Neurological symptoms include peripheral neuropathy mimicking Guillain-Barre syndrome, cognitive impairment, confusion and memory loss [5]. Other symptoms involve the gastrointestinal, genitourinary and the respiratory and cardiovascular systems [2, 3]. These manifestations of chronic, non-lethal arsenic poisoning occur at levels of 0.001 to 0.1 mg/kg/day, if exposed to inorganic arsenic > 365 days [4].

With the addition of ATO to the treatment of patients suffering from APL, clinicians must be aware of the potential side effects. We here report a case of a previously healthy woman who was diagnosed with APL and treated with ATRA-ATO who subsequently developed invalidating polyneuropathy.

Case Report

A 63-year-old, previously healthy woman was referred to the Department of Hematology at Aalborg University Hospital in June 2018 due to leucopenia and anemia. Blood samples showed hemoglobin levels of 11.1 g/dL, platelets of 154 × 10^9/L, leukocytes of 1.5 × 10^9/L, D-dimer of 15.9 mg/L, lactate dehydrogenase of 191 U/L and fibrinogen of 156 mg/dL. Bone marrow examination revealed 50% promyelocytes and fluorescence in situ hybridization (FISH) was positive of PML-RARA...
fusion gene, pathognomonic for APL. Induction treatment with ATRA-ATO was started; i.e., ATO 0.3 mg/kg intravenously day 1 - 5, and 0.25 mg/kg day 8, 11, 15, 22, 25, 29, 32 combined with ATRA 22.5 mg/m² for day 1 - 32 (induction line). Bone marrow biopsy on day 31 showed complete remission (CR) by morphology and cytogenetics and a reduction of measurable minimal residual disease (MRD) to a level of 0.1%. The patient experienced dysesthesia on her palms and plantar faces of feet but had no other side effects. Consolidation treatment included ATO of 0.3 mg/kg of day 1 - 5, in the first week, and 0.25 mg/kg two times per week for 3 consecutive weeks followed by 4 weeks without ATO combined with ATRA for day 1 - 14 and day 29 - 42. After 1 week of consolidation she developed a generalized rash, nausea and vomiting. She was administered cortisone and responded promptly, and the treatment was continued (i.e., 0.25 mg/kg two times per week for 3 consecutive weeks followed by 4 weeks of no ATO but ATRA as described above). In total, she received the induction treatment counting 285 mg of ATO followed by one consolidation treatment counting 262 mg of ATO. Bone marrow examination following the first consolidation course showed complete molecular remission of APL. The treatment with ATO was discontinued and only one of four courses of consolidation treatment with ATRA was given. However; the dysesthesia progressed over the following month and included severe paresthesia and pronounced, generalized muscular fatigue, among others leading to impaired walking function. A month later the patient still suffered from invalidating polyneuropathy, defined as a grade 3 nervous system disorder using the common terminology criteria for adverse events v3.0 (CTCAE).

Clinical examination revealed extensive sensory and motor neuropathy, primarily in the lower extremities. Spinal fluid examination, blood samples and magnetic resonance imaging (MRI) scan were normal. Nerve conduction studies (NCSs) revealed sensorimotor axonal polyneuropathy, predominantly in the lower extremities (Table 1). The patient’s total levels of arsenic (including bi-products of metabolization) in urine and blood 2 months after the last ATO dose was administered, were within the reference range of a population with a high intake of fish and shellfish. Her spouse, who shared the same lifestyle and diet as the patient, had markedly lower urine and blood arsenic levels, and were within the reference range of the general population [6]. Especially the levels of dimethylarsenic acid (DMA) were higher in the urine and blood of the patient, with levels of 21.2 µg/L and 1.57 µg/L, respectively. The spouse had levels of DMA in urine and blood at 2.84 µg/L and < 1 µg/L, respectively, which can be seen in Table 1.

Eight months following end of ATO treatment, the patient continues to suffer from peripheral neuropathy. While motor functions have slightly improved, complete loss of sensation peripherally on all extremities is persisting. The patient is still in CR and MRD negative without any further treatment.

**Discussion**

We have presented a case of a patient treated with ATO and ATRA for APL, who developed severe and invalidating arsenic-induced CTCAE grade 3 peripheral sensorimotor axonal neuropathy. In the AML-17 trial with a total of 116 patients, no peripheral neuropathy was reported [7]. The patient followed the treatment regimen from the AML-17 trial but had to discontinue ATO after the first consolidation course of four planned consolidation courses. Arsenic is a highly toxic compound, that has been used in medical applications for centuries and symptoms of intoxication are well described [2, 3]. Peripheral neuropathy and skin rash led to suspicion of ATO intoxication in the case presented, and are among the most frequent signs of intoxication. Also, the patient had NCS results consistent with severe axonal polyneuropathy, which is a rarely reported side effect to ATO treatment [5].

A study from Shen et al included 15 patients with relapsed APL treated with ATO in dosages of 10 mg/day until CR, with total induction dosages between 280 and 540 mg. In the study, ATO was discontinued for 30 days after obtaining CR. Afterwards a consolidation therapy of 10 mg ATO/day was administered for 28 days. A total (induction and consolidation) amount of ATO between 580 and 840 mg was administered. No signs of peripheral neuropathy were reported [8]. In a study from Soignet et al of 34 patients treated with ATO for relapse of APL, the induction therapy was administered with a dose of 0.15 mg/kg/day until remission or a total of 60 doses. Afterwards, one consolidation treatment of 0.15 mg/kg for 25 doses over a maximum of 35 days was given. Seventeen patients reported CTCAE grade 1 peripheral neuropathy and one patient reported CTCAE grade 3 peripheral neuropathy, reported as impaired fine motor skills and gait disturbance. The treatment was discontinued, and the neuropathy spontaneously improved within 18 days [9]. Finally, Iland et al reported one patient suffering from peripheral neuropathy in a study of 124 patients treated with ATRA, idarubicin and ATO (0.15 mg/kg daily) as initial therapy [10].

**Conclusions**

As patients with APL are now primarily treated with so-called chemo-free ATRA-ATO regimens, the question remains why some patients develop peripheral sensorimotor polyneuropathy and whether this to some degree is reversible, as the mechanism of toxicity is not well understood. Clinicians and healthcare professionals treating APL patients should be aware of this potential adverse side effect, and continuously monitoring of side effects must include specific evaluation of neurological symptoms and prompt intervention when evident. Dose reduction or stop of ATO treatment should be considered in patients displaying signs of peripheral neuropathy.

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None to declare.
| Nerve Conduction Studies (All Tests Are Performed on the Right Side) | October 18 | January 19 |
|--------------------------|------------|------------|
|                          | Latency (ms) | Amplitude (mV) | Conduction velocity (m/s) | Latency (ms) | Amplitude (mV) | Conduction velocity (m/s) |
| **Motor nerve conduction studies** | | | | | | |
| **Median nerve** | | | | | | |
| Wrist | Musculus abductor pollicis brevis-wrist | 3.6 | 7.1 | 3.8 | 7.7 |
| Elbow | Wrist-elbow | 8.1 | 6.9 | 49 | 7.9 | 7.3 | 50 |
| **Ulnar nerve** | | | | | | |
| Wrist | Musculus abductor digitii minimi-wrist | 2.8 | 9.2 | 2.1 | 9 |
| Below elbow | Wrist-below elbow | 5.2 | 7.3 | 63 | 5.6 | 8.6 | 64 |
| Proximal elbow | Below elbow-proximal elbow | 7.5 | 8.2 | 48 | 7 | 8.7 | 57 |
| **Tibial nerve** | | | | | | |
| Ankle | Musculus abductor hallucis-ankle | 3.9 | 1.4 | 3.8 | 2.8 |
| Popliteal fossa | Ankle-popliteal fossa | 12.4 | 0.1 | 43 | 13.2 | 0.5 | 42 |
| **Peroneus profundus nerve** | | | | | | |
| Ankle | Musculus extensor digiti brevis-ankle | 3.7 | 0.4 | 5.4 | 0.5 |
| Capitulum fibulae | Ankle-caput fibulae | 11.9 | 0.3 | 35 | 12.1 | 0.6 | 39 |
| Poples | Caput fibulae-poples | 14.4 | 0.3 | 38 | 13.9 | 0.6 | 49 |
| **Sensory nerve conduction studies** | | | | | | |
| **Median nerve** | | | | | | |
| Index finger (F2) | Wrist-index finger (F2) | 2.7 | 4.8 | 56 | 2.8 | 8 | 54 |
| Middle finger (F3) | Wrist-middle finger (F3) | 2.8 | 4.2 | 56 | 3 | 6.7 | 52 |
| Ulnar nerve | Wrist-little finger (F5) | 2.6 | 4 | 54 | 2.3 | 8.3 | 54 |
| Radial nerve | Forearm-tabatiere | 1.1 | 13.9 | 75 | 1.8 | 7.8 | 68 |
| Peroneus superior nerve | Lateral crus-ankle | 2.2 | 0.7 | 39 | 2.4 | 1.2 | 38 |
| Sural nerve | Sura-lateral malleolus | UR | UR | UR | NR | NR | NR |

UR: Uncertain response; NR: No response.
Conflict of Interest

None to declare.

Informed Consent

Patient's informed consent for publication of this report was obtained.

Author Contributions

M. Severinsen and A. Roug treated the patient. M. Severinsen conceived of the presented idea. S. Helso wrote the manuscript with support from M. Severinsen, A. Roug, M. Mork and E. Maksten. All authors discussed the results and contributed to the final manuscript.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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