Arsenic Trioxide in Acute Promyelocytic Leukemia and Associated Bone Marrow Changes

Asim Ahmad MD
Introduction

- Arsenic trioxide (ATO) approved by the Food and Drug Administration for the treatment of APL

- In animal models, ATO has been shown to cause bone remodeling likely through changes in osteoblast differentiation and function (1)

- We noted that after using ATO for treatment of APL, post therapy bone marrow biopsies showed increased osteoblast rimming of the bony trabecular.
Case Presentation

- 41 year old male with history of type II diabetes who presented with easy bruising, dyspnea on exertion, and fatigue
- He was diagnosed with APL and began induction therapy with all trans retinoic acid and ATO.
- Day 30 bone marrow demonstrated persistent 15,17 translocation. Induction therapy was continued.
- On Day 62 no clonal abnormalities by FISH, received 4 months of ATO 0.15 mg/kg Monday through Friday consolidation therapy
- Bone Marrow Biopsy performed 5 months after ATO cessation to evaluate for rimming.

<table>
<thead>
<tr>
<th>Slide Number</th>
<th>Time from ATO Exposure</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Baseline</td>
<td>0% Osteoblastic rimming</td>
</tr>
<tr>
<td>2</td>
<td>Day 30 bone marrow (receiving ATO)</td>
<td>40% Osteoblastic Rimming</td>
</tr>
<tr>
<td>3</td>
<td>Day 62 bone marrow days (receiving ATO)</td>
<td>70% Osteoblastic Rimming</td>
</tr>
<tr>
<td>4</td>
<td>5 Months Post ATO use</td>
<td>0% Osteoblastic Rimming</td>
</tr>
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Day 30 Bone Marrow Biopsy
Day 62 Bone Marrow Biopsy
Case Number Two

- A 3 year old female who presented with a history of easy bruising and petechiae.
- Bone marrow performed and confirmed diagnoses of APL.
- She was treated under Children’s Oncology Group protocol AAML0631.
- Following maintenance cycle 5, she underwent bone marrow biopsy.
- Bone marrow biopsies performed thereafter showed persistent decreases in the percent of osteoblastic rimming.

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<tbody>
<tr>
<td>1</td>
<td>Baseline</td>
<td>No osteoblastic rimming</td>
</tr>
<tr>
<td>2</td>
<td>One month</td>
<td>60% osteoblastic rimming cells</td>
</tr>
<tr>
<td>3</td>
<td>2 months</td>
<td>40% osteoblastic rimming</td>
</tr>
<tr>
<td>4</td>
<td>8 months</td>
<td>20% osteoblastic rimming</td>
</tr>
<tr>
<td>5</td>
<td>13 months</td>
<td>20% osteoblastic rimming</td>
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Two Additional Cases

- A 30 year old female with past medical history of provoked lower extremity blood clot was noted on routine CBC to be leukopenic (WBC count of 0.8 X 10^9/l with absolute neutrophil count of 108). Her fibrinogen was low at 103 mg/dl. Platelet count was over 40K. Bone Marrow biopsy demonstrated APL and patient was treated with induction 7+3 and all trans retinoic acid. Two months later she underwent ATO consolidation - 0.15 mg/kg Monday through Friday for 5 weeks.

- A 69 Year old man with past medical history of COPD, CAD, and DM, was found incidentally on CBC to be pancytopenic including a WBC of 1.4 X10^9/l with an absolute neutrophil count of 60, platelet count was over 40K. He underwent bone marrow biopsy which demonstrated APL and was induced with all trans retinoic acid and ATO.
Conclusion

- ATO represents a cornerstone in the therapy of APL.
- Past researchers have shown an association with ATO and bone remodeling in animal models, similar findings have yet to be reported in humans.
- We highlight a pivotal finding of increased osteoblast rimming of bone marrow core biopsies following ATO therapy.
- This finding was noted in a diverse group of patients with ages ranging from 3 years to 69 years.
  - It was appreciated in both men and women and does not appear to be related to morphology, immunophenotype or molecular genetics of the leukemia.
  - It was appreciated in both men and women. Adults and Children. And did not seem to be influenced by the morphology, immunophenotype, or molecular genetics of the leukemia.
Hu et al. have described, in mouse models, that ATO therapy leads to decreased osteoblast mineralization by decreasing alkaline phosphatase production (1).

Of note, the patient in case one had a mild increase in serum phosphorous level following arsenic therapy. It has been noted that arsenic exposure can cause hyperphosphatemia in animal models, whether a similar process is occurring here also warrants further investigation (2).