Cost-effectiveness Analysis of Arsenic Trioxide for the Treatment of Patients with Acute Promyelocytic Leukemia in the US

**Background**

- Acute promyelocytic leukemia (APL) is a distinct subtype of acute myeloid leukemia (AML) with ~1,000-1,500 new cases in the US per year.
- Arsenic trioxide (ATO) is currently licensed for the treatment of APL for patients who are refractory to, or have relapsed from previous treatment with all-trans retinoic acid (ATRA) and anthracycline-based chemotherapy.
- Current 1st-line treatment in the US (NCICCN):
  - ATO+ATRA:
    - Induction with ATO+ATRA
    - Consolidation with ATO+ATRA
  - AIDA:
    - ATRAX+Daunubiotic
    - ATRA
  - ATO+Daunubiotic
  - ATRA+Daunubiotic
- Overall, studies indicate that ATO is a possible 1st-line alternative option for APL.

**Objective**

To estimate the cost-effectiveness of ATO in 1st-line in the treatment of APL using the third-party perspective in the US.

**Methods**

**Target Population**

- Based on the clinical trial populations: patients are 45 years old at model entry based on median age of APL patients at first diagnosis.
- Comparators:
  - See Figure 1 below for choice of therapy
  - Time Horizon:
    - 55 years until patients reach 100 years of age or die
- Model Structure:
  - A four-state Markov ("state-transition") model was developed based on the natural history and outcomes of APL using a 1 month cycle length (Figure 2).
  - All patients begin in the "stable disease" health state and stay in this state while receiving their initial therapy until they experience a disease event or die.

**Mortality**

- Age-specific mortality rates for the US population were estimated to use the probability of dying for all other causes.

**Transition probabilities (EFS) (event-free survival) and OS** (see Table 1)

- Monthly probabilities of experiencing an event were estimated from Lo-Cocco 2011F for the AIDA and ATO + ATRA treatment arms.
- ATRA + ATRA-Chemo arm used results from Powell 2010

**Adverse event rates**

- Adverse event rates were obtained from published sources:
  - ATO + ATRA: Lo-Cocco 2013
  - AIDA - Lo-Cocco 2013
  - ATRA + ATRA-Chemo: Powell 2010

**Costs**

- Costs of the treatment regimens were estimated using the standard wholesale acquisition costs (WAC) in the US.
- Costs for ATO or ATRA + AIDA were based on the treatment regimen as outlined in Lo-Cocco 2013.
- For the ATRA + ATRA-Chemo arm, the analysis was performed using the costs from Powell 2010.
- Calibration was used (Microsoft Excel Solver) to ensure that the transition between the observed data (clinical trials) and predicted data (model-produced outcomes) is minimized.
- See Tables 3 and 4
- Utilities (see Table 2)

**Results**

**Figure 4. Base case results**

- Regimen
  - Total drug costs ($): $136,170
  - BC: $18,500
  - Drug costs: $117,670
  - BC: $16,800
  - Drug cost of ATO Consolidation (1st Line): $6,621
  - BC: $8,828

**Methods (cont.)**

**Figure 3. Tornado diagram ATO vs AIDA**

- Probabilistic sensitivity analysis
  - Using the Markov cohort-model, a second-order PSA with 1,000 samples was conducted
  - At a threshold of $9,000 per QALY, the probability of ATO being cost-effective was 83%.
  - At a threshold of $14,000 per QALY, the probability of ATO being cost-effective was 100%.

**Conclusions**

- Arsenic Trioxide provides clinical results, with improvements in quality of life and survival
- Arsenic Trioxide is cost-effective with a base-case ICER of $5,614 compared to AIDA in the 1st-line setting
  - Versus the AIDA regimen, the ATO regimen displayed a ~75% increase in QALYs with a roughly 35% increase in costs
- Arsenic Trioxide is cost-effective with a base-case ICER of $5,148 compared to ATRA + ATRA-Chemo in 1st-line
  - Versus ATRA + ATRA-Chemo regime, the ATO regimen has more than double the QALYs, with an only 40% increase in costs.
- Extensive deterministic and probabilistic sensitivity analyses show that ATO is 100% cost-effective at willingness-to-pay thresholds of $14,000 and higher.
- Overall, the shorter and better-tolerated regimen of ATO+AIDA is a highly cost-effective strategy compared to ATRA-Chemothrapy or AIDA in the treatment of newly diagnosed low-to-intermediate risk APL patients.

**References**

- Waltham, MA, USA. 2013
- Waltham, MA, USA, 2013
- Waltham, MA, USA. 2013
- Waltham, MA, USA. 2013
- Waltham, MA, USA. 2013
- Waltham, MA, USA. 2013
- Waltham, MA, USA. 2013
- Waltham, MA, USA. 2013
- Waltham, MA, USA. 2013
- Waltham, MA, USA. 2013

---

**Table 1. Clinical Transition Probabilities**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Numerator Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATO + ATRA (Lo-Cocco 2013)</td>
<td>ATRA + ATRA-Chemo</td>
</tr>
<tr>
<td>AIDA</td>
<td>(Powell 2010)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Transition Probabilities, monthly (1st-line)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATO + ATRA (Lo-Cocco 2013)</td>
</tr>
<tr>
<td>AIDA</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Probability of an event</th>
<th>0.0084</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability of death from disease state (below)</td>
<td></td>
</tr>
<tr>
<td>0.0058</td>
<td>0.00444</td>
</tr>
</tbody>
</table>

**Table 2. Utilities**

<table>
<thead>
<tr>
<th>Model Parameter</th>
<th>Value</th>
<th>Data Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATO/IDAS efficacy values</td>
<td>Varies by age</td>
<td>Schmidt 2010</td>
</tr>
<tr>
<td>Background US utility values</td>
<td>Varies by age</td>
<td>Hammer 2006</td>
</tr>
<tr>
<td>Progression-free: 1st-line treatment</td>
<td>0.78</td>
<td></td>
</tr>
<tr>
<td>Progression-free: 2nd-line treatment</td>
<td>0.57</td>
<td></td>
</tr>
<tr>
<td>Progression-free: 3rd-line treatment</td>
<td>0.47</td>
<td></td>
</tr>
<tr>
<td>OS</td>
<td>0.78</td>
<td></td>
</tr>
</tbody>
</table>

---

**Table 2. Treatment costs considered in the model**

<table>
<thead>
<tr>
<th>Treatment Phase</th>
<th>Stable Disease (1st line)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATO + ATRA</td>
<td>$20,503</td>
</tr>
<tr>
<td>AIDA</td>
<td>$778</td>
</tr>
<tr>
<td>ATRA + ATRA-Chemo</td>
<td>$778</td>
</tr>
</tbody>
</table>

| Induction | $20,503 | $20,503 | $20,503 |
| Consolation | $778 | $778 | $778 |
| Maintenance | $40 | $40 | $40 |
| Drug costs per treatment arm | $61,797 | $13,146 | $38,308 |

**Table 3. Drug cost:**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cost of Fever of Unknown Origin - Consolidation ($10,917-$6,550); BC: $8,734</th>
<th>Cost of Fever of Unknown Origin - Consolidation ($10,917-$6,550); BC: $8,734</th>
<th>Cost of Fever of Unknown Origin - Consolidation ($10,917-$6,550); BC: $8,734</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATO</td>
<td>$10,917</td>
<td>$6,550</td>
<td>$8,734</td>
</tr>
<tr>
<td>AIDA</td>
<td>$136,170</td>
<td>$20,503</td>
<td>$20,503</td>
</tr>
<tr>
<td>ATRA + ATRA-Chemo</td>
<td>$136,170</td>
<td>$20,503</td>
<td>$20,503</td>
</tr>
</tbody>
</table>

---

**Table 4. Adverse event costs considered in the model**

<table>
<thead>
<tr>
<th>Treatment Phase</th>
<th>Adverse Event</th>
<th>Event Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction</td>
<td>$200</td>
<td>$200</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>$0</td>
<td>$0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>$0</td>
<td>$0</td>
</tr>
<tr>
<td>Hepatic toxicity</td>
<td>$0</td>
<td>$0</td>
</tr>
<tr>
<td>Consolation</td>
<td>$8,734</td>
<td>$8,734</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>$0</td>
<td>$0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>$1,376</td>
<td>$1,376</td>
</tr>
<tr>
<td>Hepatic toxicity</td>
<td>$6,382</td>
<td>$6,382</td>
</tr>
<tr>
<td>2 years post-induction</td>
<td>$20,503</td>
<td>$20,503</td>
</tr>
<tr>
<td>Late secondary leukemias</td>
<td>$20,503</td>
<td>$20,503</td>
</tr>
<tr>
<td>AE costs incurred during the induction phase were reimbursed under the induction DRG</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

**Figure 2. Markov Bubble Diagram**

- 1st-line Table Disease
- 2nd-line Disease Event (in relative survival achieved)
- Death

---

**Figure 1. Choice of therapy**

- 1st-line ATRA + ATRA
- 2nd-line AIDA

---

**Figure 3. Tornado diagram ATO vs AIDA**

- Probabilistic sensitivity analysis
  - Using the Markov cohort-model, a second-order PSA with 1,000 samples was conducted
  - At a threshold of $9,000 per QALY, the probability of ATO being cost-effective was 83%.
  - At a threshold of $14,000 per QALY, the probability of ATO being cost-effective was 100%.

---

**Figure 4. Tornado diagram ATO vs. ATRA + ATRA-Chemo**

- Arsenic Trioxide provides clinical results, with improvements in quality of life and survival
- Arsenic Trioxide is cost-effective with a base-case ICER of $5,614 compared to AIDA in the 1st-line setting
  - Versus the AIDA regimen, the ATO regimen displayed a ~75% increase in QALYs with a roughly 35% increase in costs
- Arsenic Trioxide is cost-effective with a base-case ICER of $5,148 compared to ATRA + ATRA-Chemo in 1st-line
  - Versus ATRA + ATRA-Chemo regime, the ATO regimen has more than double the QALYs, with an only 40% increase in costs.
- Extensive deterministic and probabilistic sensitivity analyses show that ATO is 100% cost-effective at willingness-to-pay thresholds of $14,000 and higher.
- Overall, the shorter and better-tolerated regimen of ATO+AIDA is a highly cost-effective strategy compared to ATRA-Chemothrapy or AIDA in the treatment of newly diagnosed low-to-intermediate risk APL patients.