Advances in the Treatment of APL in Children

SLOP

Vina del Mar—April 2014
Outline

• Advances in supportive care of pediatric acute promyelocytic leukemia (APL)
• Advances in specific treatment of pediatric APL
SLE por Riesgo, abandono como evento (No. 75)

Curva de supervivencia de POND

- **efs_ae - Bajo = 35**
- **efs_ae - Alto = 40**

Porcentaje

Años
<table>
<thead>
<tr>
<th></th>
<th>Bajo Riesgo No.(35)</th>
<th></th>
<th>Alto Riesgo No.(40)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Primer Evento</td>
<td>%</td>
<td>%</td>
<td>Primer Evento</td>
</tr>
<tr>
<td>Vivo</td>
<td>15</td>
<td>43</td>
<td>57</td>
<td>14</td>
</tr>
<tr>
<td>Abandono</td>
<td>4</td>
<td>11.5</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Enfermedad Resistente</td>
<td>1</td>
<td>3</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Recaída</td>
<td>11</td>
<td>31</td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>Fallecido</td>
<td>4</td>
<td>11.5</td>
<td>40</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>35</td>
<td>100</td>
<td>100</td>
<td>40</td>
</tr>
</tbody>
</table>
Case Presentation

13-year old girl with altered mental status

- 2 weeks prior had sinus symptoms
- Progressive weakness and body aches
- Eye pain and blurry vision
- Somnolent and confused
- Syncope in bathroom followed by emesis
Physical Examination

- **Vitals:** T37.7, HR 127, BP 148/78, RR20
- **General:** Asleep, combative when aroused; obese
- **HEENT:** Pupils 3mm, reactive, equal; bilateral papilledema and retinal hemorrhages
- **Neurological:** Uncooperative, difficult to understand speech
Laboratory Studies

• **WBC** count 93.7 x $10^9$/L; ANC 2.8 x $10^9$/L; Hgb 6.3 g/dL; platelet count 45.0$^9$/dL; differential: 2% segs, 3% lymph, 1% mono, 88% blast

• Coagulation: PT 20 sec, INR 1.86, aPTT 25.2 sec, fibrinogen 114 mg/dL

• Uric acid 5.2 mg/dL
Intracranial Ischemic Infarcts
Intracranial Ischemic Infarcts
Coagulopathy in APL

- It manifests as hemorrhage or thrombosis
- Mechanism is not known
- Activating of the coagulation system
- Non-specific protease stimulation
- The predominant feature at diagnosis is fibrinolysis
Management of Coagulopathy

• Blood Products
  – Platelets (> 50 x 10⁹/l)
  – Fibrinogen (>100 mg/dL)

• No proven benefit for use of heparin or anti-fibrinolytic agents

• Anti-fibrinolytic agents when combined with ATRA could increase the risk of thrombotic complications

• Leukapheresis is not recommended for hyperleukocytosis
Coagulopathy

Fibrinogen/dL

Platelet count x 10^9/L
Induction Atra
Should ATRA be held?

- Day 3: Tachypnea and $O_2$ saturation drop
- Day 3: Started dexamethasone
- Day 4: Oxygen via nasal cannula
- Day 5: Transitioned to high-frequency nasal cannula (HFNC)
- Day 7: Off HFNC, fever resolved
- Steroids weaned over 4 days
Induction: ATRA + Idarubicin (AAML0631)
Pathogenesis

Luesink M. Br J Haematol. 2010 151:209-20
Management of Differentiation Syndrome

• Initiate dexamethasone at the very earliest suspicion of RA syndrome

• Temporary discontinuation of ATRA only in case of severe RA syndrome

• Prophylaxis with prednisone 1 mg/kg/day
Induction: Continuing ATRA

- Weaned off oxygen
- WBC decreased
- Intense rehab for strokes, becoming more interactive
- Day 15: new spots in visual fields, L>R. BP 160/100
- MRI- prior infarcts, no new findings
- LP- opening pressure too high to measure
Pseudotumor Cerebri

- More common in children
- Impair of CSF absorption at the level of the arachnoid villi or granulation
- Headaches
- Diplopia
- 6\textsuperscript{th} cranial nerve palsy
- Papilledema
Pseudotumor Cerebri
( Idiopathic Intracranial Hypertension )

• Stopped ATRA
• Started dexamethasone and Diamox
• Serial therapeutic taps
• ATRA restarted at 75% dose when opening pressure decreased to goal 30-35mm H2O
• Continued Diamox through induction
Evolution of Intracranial Ischemic Infarcts

3.9.2012

3.23.2012

6.25.2012
Specific Management of APL
Historic Halmarkers

**Induction**

- Patients receiving ATRA had significantly greater EFS compared with those in chemotherapy-only arms
- ATRA plus chemotherapy was superior that ATRA alone, particularly in individuals with WBC > 10,000/µL
# APL European Group

## Role of Chemotherapy in Induction

<table>
<thead>
<tr>
<th>N (%) Median</th>
<th>ATRA→CT</th>
<th>ATRA+CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>122</td>
<td>184</td>
</tr>
<tr>
<td>Male sex</td>
<td>59 (48.4)</td>
<td>87 (47.3)</td>
</tr>
<tr>
<td>Age, y (range)</td>
<td>46 (35-54)</td>
<td>44 (33-55)</td>
</tr>
<tr>
<td>WBC count, 10⁹/L (range)</td>
<td>1.3 (0.8-2.25)</td>
<td>1.4 (0.9-2.5)</td>
</tr>
<tr>
<td>CR: N (%)</td>
<td>113 (92.6)</td>
<td>177 (96.2)</td>
</tr>
<tr>
<td>10-year CI of relapse</td>
<td>21.6%</td>
<td>13.2%</td>
</tr>
<tr>
<td>10-year CI of deaths in CR</td>
<td>6.6%</td>
<td>6.7%</td>
</tr>
<tr>
<td>10-year EFS</td>
<td>64.4%</td>
<td>76.3%</td>
</tr>
<tr>
<td>10-year survival</td>
<td>81.8%</td>
<td>85.0%</td>
</tr>
</tbody>
</table>

Cytarabine in Consolidation LPA99 and 2005

Induction Therapy (AIDA)

Consolidation Therapy

LPA99
- IDA 7 mg/m²/d x 4
- ATRA 45 mg/m²/d x 15

LPA2005
- IDA 5 mg/m²/d x 4
- Ara-C 1000 mg/m²/d x 4
- ATRA 45 mg/m²/d x 15

MTZ 10 mg/m²/d x 5
- ATRA 45 mg/m²/d x 15

MTZ 10 mg/m²/d x 5
- ATRA 45 mg/m²/d x 15

IDA 12 mg/m²/d x 2
- ATRA 45 mg/m²/d x 15

IDA 12 mg/m²/d x 1
- Ara-C 150 mg/m²/8h x 4
- ATRA 45 mg/m²/d x 15

Maintenance Therapy (2 years)

Sanz M A et al. Blood 2010;115:5137-5146
Cumulative Incidence of Relapse in High-Risk Patients according to PETHEMA Trial

Sanz M A et al. Blood 2010;115:5137-5146
# Long-Term Outcome APL European Group

## Role of Maintenance

<table>
<thead>
<tr>
<th></th>
<th>ATRA</th>
<th>No maintenance</th>
<th>ATRA+CT</th>
<th>CT alone</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number</strong></td>
<td>76</td>
<td>79</td>
<td>129</td>
<td>117</td>
<td></td>
</tr>
<tr>
<td><strong>Relapse</strong></td>
<td>26</td>
<td>35</td>
<td>18</td>
<td>29</td>
<td>&lt; .001</td>
</tr>
<tr>
<td></td>
<td>33.0%</td>
<td>43.2%</td>
<td>13.4%</td>
<td>23.4%</td>
<td></td>
</tr>
<tr>
<td><strong>10-year EFS</strong></td>
<td>62.9%</td>
<td>51.4%</td>
<td>79.7%</td>
<td>72.6%</td>
<td>&lt; .001</td>
</tr>
<tr>
<td><strong>10-year OS</strong></td>
<td>88.0%</td>
<td>74.4%</td>
<td>94.4%</td>
<td>93.4%</td>
<td></td>
</tr>
</tbody>
</table>

Maintenance

• ATRA-based maintenance shown to reduce relapse
• It is uncertain whether patients who achieve complete remission after induction and are negative for the PML/RARα fusion gene after consolidation benefit from maintenance
Overall survival of Children Treated on the PATHEMA Trials

Cumulative Anthracycline Dosage in Contemporary Pediatric AML trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Anthracycline mg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRC10/12</td>
<td>550-580</td>
</tr>
<tr>
<td>France-93</td>
<td>495</td>
</tr>
<tr>
<td>AIEOP-93</td>
<td>650</td>
</tr>
<tr>
<td>CCG-2911</td>
<td>405</td>
</tr>
<tr>
<td>BFM-93</td>
<td>350</td>
</tr>
<tr>
<td>SHOP</td>
<td>650-750</td>
</tr>
<tr>
<td>Ref.</td>
<td>No. of Patients</td>
</tr>
<tr>
<td>------</td>
<td>----------------</td>
</tr>
<tr>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>21</td>
</tr>
<tr>
<td>2</td>
<td>56</td>
</tr>
<tr>
<td>3</td>
<td>72</td>
</tr>
<tr>
<td>4</td>
<td>97</td>
</tr>
<tr>
<td>5</td>
<td>44</td>
</tr>
</tbody>
</table>

Consolidation with ATO significantly improves RR, EFS and OS among patients with newly diagnosed APL (US Intergroup C9710 trial)

Event-free survival

Time (months)

Event-free survival

81%

66%

p=0.001

p=0.09

ATO

No ATO

Pediatric

Powell et al. ASCO 2007
Arсенный Триоксид в Индукционной Терапии
Интерпретация Доказательств

• В некоторых странах, где местное производство арсенальных соединений существует, это приводит к леченю многих пациентов с APL

• Отличные предварительные результаты от относительно небольших и выбранных серий в одних учреждениях

• Клинические испытания для определения эффективности, безопасности и экономической эффективности заслуживают одобрения
156 patients with low/intermediate risk were randomized
Probability of Event-Free Survival

![Graph showing the probability of event-free survival over months since diagnosis for ATRA–arsenic trioxide and ATRA–chemotherapy treatments. The graph includes a table showing the number of patients at risk for each group at various time points: 76 at 0 months, 73 at 12 months, 72 at 24 months, 28 at 36 months, and 5 at 60 months for ATRA–arsenic trioxide; and 77 at 0 months, 68 at 12 months, 65 at 24 months, 27 at 36 months, and 7 at 60 months for ATRA–chemotherapy. The statistical significance is indicated with P = 0.02.]
Probability of Overall Survival

![Graph showing the probability of overall survival over months since diagnosis for two treatment groups: ATRA–arsenic trioxide and ATRA–chemotherapy. The graph indicates a statistically significant difference, with a P-value of 0.02.]

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>ATRA–arsenic trioxide</th>
<th>ATRA–chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>77</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td>73</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td>73</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>7</td>
</tr>
</tbody>
</table>
Probability of Relapse


Probability of Relapse

P = 0.24

No. at Risk

<table>
<thead>
<tr>
<th>Group</th>
<th>Risk</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATRA–arsenic trioxide</td>
<td>76</td>
<td>73</td>
<td>68</td>
<td>26</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>ATRA–chemotherapy</td>
<td>73</td>
<td>68</td>
<td>63</td>
<td>23</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>
Hematologic Toxic Effects

Future Directions

• Integration of ATO in front-line treatment in childhood APL
• Oral ATO
• Liposomal ATRA
• Other retinoid drugs: Tamibarotene
Conclusions

• APL in children is highly curable with current strategies
• Early mortality and long-term sequelae remain concerns particularly in low-income countries
• Continue research to understand the pathogenesis of early complication is necessary
• Treatment optimization to decrease the potential for anthracycline-cardiac toxicity