Safety and efficacy of ATRA with Arsenic Trioxide combination therapy in Acute Promyelocytic Leukemia

Department of Internal Medicine, Hematology*, Post Graduate Institute of Medical Education & Research, Chandigarh 160012, India.
Website: http://pgIMER.nic.in; gurufall@gmail.com

Introduction
- Acute Promyelocytic Leukemia is distinct type of AML
- Characterised by reciprocal translocation of 15:17.
- Formation of PML-RARα gene product
- Life threatening coagulopathy
- Requires immediate treatment
- All-trans Retinoic Acid (ATRA): first molecular targeted therapy.
- Standard therapy: ATRA plus Chemotherapy
- Single agent Arsenic trioxide: promising results
- Long term cure rates of 70-80%

Objectives
- To study the safety and efficacy of ATRA with Arsenic Trioxide combination therapy.
- Attractive treatment option without use of chemotherapy
- Distinguish action on degradation of PML-RARα
- High successful induction rates
- Early morphological recovery of bone marrow
- Early recovery of platelets
- Early amelioration of coagulopathy

Methods
- Retrospective study.
- Patients who were given therapy: Poor performance status, who did not give consent for chemotherapy.
- Diagnosis: Bone marrow examination, Cytogenetics, k(15;17)/PML-RARα by RT-PCR
- Dose in induction therapy: ATRA 25mg/m², ATO 0.15mg/kg/d, 5 days/week.
- Continue till hematological Remission (ANC>1500, ACP>10000). Check marrow.
- Drug free period of 4 weeks.
- Consolidation therapy: Similar to induction for 3 times (ATRA for 4 week, Arsenic trioxide 26 injection)
- Check for molecular remission before 1st consolidation.
- Maintenance therapy for 2 years.
- ATRA 25mg/m²: for 15 days every 3rd month, mercaptopurine 50mg/m², methotrexate 25mg/m² weekly.
- Supportive therapy with platelets and fresh frozen plasma.

Results and Discussion

Risk Stratification: High risk: WBC>10,000/ul, Platelet<40,000/ul
Standard risk: WBC<10,000, Platelet>40,000/ul

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Induction Deaths</th>
<th>Hematological Remission in days (Median, range)</th>
<th>Successful Induction</th>
<th>PML-RARα absence</th>
<th>Morphological relapse</th>
<th>Deaths in remission</th>
<th>Maintainance of treatment</th>
<th>Follow up</th>
<th>Event free duration in months (Median, range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>7</td>
<td>35 (15-49)</td>
<td>85%</td>
<td>100%</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>18</td>
<td>17 (10-37)</td>
</tr>
</tbody>
</table>

Adverse Effects
- ATRA Syndrome: 36%
- ATRA vasculitis: 0%
- Qtc Prolongation: 0%

Discussion
- Well tolerated regimen (Safe)
- High Induction Success (Efficacious)

Limitations
- Retrospective study
- Randomized controlled trial required

Conclusions
- Combination of ATRA with Arsenic Trioxide appears to be well tolerated in patients with APL with minimum side effects
- Efficacious in high risk patients also
- Attractive treatment option for the patients in the developing countries where mortality related to infection is amajor problem.

References:
4. Elsay et al: Use of all-trans retinoic acid plus arsenic trioxide as alternative to chemotherapy in untreated acute promyelocytic leukemia. Blood 2005:10;4006