Acute Promyelocytic Leukemia: Current Management with Emphasis on Prevention of Induction Mortality

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Multiple Choice #1
Which of the following leukemias has a very high chance of being cured?

• ALL
• CLL
• AML
• APL
Multiple Choice #2

The most common causes of death in APL are

• Bleeding only
• Bleeding, infection and Differentiation syndrome
• Infection and bleeding
• Differentiation syndrome only

Multiple Choice #3

Active agents in the treatment of APL are -

• Anthracyclines
• Arsenic trioxide
• ATRA
• Methotrexate
• All of the above
APL Therapy: History

First description: Hyperacute fatal illness associated with hemorrhagic syndrome

Daunorubicin in APL

In vivo leukemic cell differentiation

Discovery t(15;17) in APL

ATRA therapy

ATRA + CT

ATO frontline

ATO in relapse

ATO + ATO ± GO


HIGHLY FATAL  HIGHLY CURABLE

APL - Incidence

- APL is an uncommon disease with approximately 800-1000 new cases per year in the US
- It is more frequent in Italy, Spain and Latin America
- Rare below the age of 10
- Most common between the ages of 20 and 60
- Highly effective treatments are available such as Al-Trans Retinoic Acid (ATRA), Arsenic Trioxide, anthracyclines and supportive care
APL Survival in Large Cooperative Group Trials

Overall Survival

Overall Survival

SEER DATA 1975-2008

Cumulative relative survival ratio
Population Wide Survival in the US

- Survival of 90% in multi-center trials is not a reflection of the outcome in the general population. **Death rate of 5 to 10% is an underestimate.**
- Recent analysis of US SEER data from 2000 to 2008 by investigators from MD Anderson showed 71% survival at 1 year and 64% at 5 years
- Current trials that are changing sequence, adding new drugs, withholding maintenance will only have a minimal effect on the survival
- The biggest impact will be made by decreasing early deaths

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Early Deaths in APL (Day 1 to 30)

<table>
<thead>
<tr>
<th>Study</th>
<th>Total patients</th>
<th>Patients died</th>
<th>Mortality rate</th>
<th>Percentage of patients with hemorrhage in early death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood (2009)</td>
<td>134</td>
<td>43</td>
<td>32%</td>
<td>66</td>
</tr>
<tr>
<td>Ankara &amp; Kuru (2010)</td>
<td>49</td>
<td>20</td>
<td>40%</td>
<td>65</td>
</tr>
<tr>
<td>Swedish registry (2013)</td>
<td>103</td>
<td>30</td>
<td>29%</td>
<td>41</td>
</tr>
<tr>
<td>SEER data(2013)</td>
<td>1400</td>
<td>230</td>
<td>17%G44% (m &gt; 55yr)</td>
<td>Not discussed</td>
</tr>
<tr>
<td>AIIMS, India</td>
<td>33</td>
<td>6</td>
<td>10.1</td>
<td>58% of total patients during induction</td>
</tr>
<tr>
<td>Stanford (2012)</td>
<td>70</td>
<td>19</td>
<td>26%</td>
<td>54</td>
</tr>
<tr>
<td>ORÜ (four center)</td>
<td>19</td>
<td>7</td>
<td>37%</td>
<td>57</td>
</tr>
<tr>
<td>ASCO 2012</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>German, &lt;60 years (2013)</td>
<td>91</td>
<td>24</td>
<td>26%</td>
<td>Not discussed</td>
</tr>
<tr>
<td>Japan &gt;65% years Hiroshima(2013)</td>
<td>32</td>
<td>7</td>
<td>21.3%</td>
<td>Not discussed</td>
</tr>
</tbody>
</table>
High Induction Mortality at GRU

- 19 patients were seen between 7/2005 and 6/2009
- 1 patient refused treatment and opted to receive hospice care
- 7 patients died during induction - 37% mortality rate
- 11 patients are being followed and all of them are in molecular remission with no relapses thus far and presumed cured
- Patients who survive induction have a 95% chance of cure

Methods Used to Decrease Early Deaths

- Reviewed the literature
- Reviewed all the patient charts
- Attended National meetings and talked to experts
- Attended the International APL meeting in Rome
- Obtained an external consultant to review our death charts
- Identified the 3 main causes of death in the first month - **BLEEDING, DIFFERENTIATION SYNDROME AND INFECTION**
- Implemented a proactive simple program to decrease Early deaths – at a point when the rest of the country did not recognize this as a problem.
Strategy (At GRU)

- Developed a simple 1.5 page treatment algorithm
- Quick diagnosis
- Ad hoc meeting and treatment planning
- Rapid initiation of therapy
- Aggressive management of coagulopathy
- Prevention of Differentiation syndrome; early recognition and management of ATRA syndrome
- Prophylaxis and aggressive treatment of infections
- Implemented in 2010

Strategy At Affiliate Sites

- Affiliates contact us when a patient is diagnosed with APL
- Email or fax our algorithm
- Discuss patient with treating physician and recommend a treatment plan
- Follow up by phone, email or texting at least 3 to 4 times in the first 10 days—during which 70% of the deaths take place.
- Why don’t the patients get transferred to a more experienced center??
Work Up

• CBC, CMP, DIC Panel- Fibrinogen, D-Dimers, PT/PTT- twice a day until all clinical coagulopathy resolves.

• Bone Marrow examination, Cytogenetics, FISH for 15:17, PCR for PML-RAR alpha

• Echocardiogram

• PICC Line; No invasive procedures

Supportive Care

• Tumor lysis prophylaxis

• Antibacterial Prophylaxis - Levofloxacin 500 qd

• Antifungal prophylaxis - Voriconazole 200 po bid or posaconazole 200 po tid

• Antiviral prophylaxis – Acyclovir 400 bid

• Keep Hb in the 8 range

• APL IS A MEDICAL EMERGENCY. TREATMENT WITH ATRA SHOULD BE STARTED ASAP.
Treatment of Coagulopathy

• Coagulopathy is a major problem. Procoagulants released by the leukemia cells and fibrinolysis.
• Intracranial, pulmonary and GI Bleeding
• Treatment with ATRA should start ASAP
• Keep platelets above 50k
• Keep Fibrinogen above 150
• If there is clinical evidence of bleeding, give FFP twice a day as you are starting ATRA and Chemotherapy till bleeding resolves.
• After all clinical and lab coagulopathy resolves, blood product support is like any other leukemias

Differentiation Syndrome

• Dyspnea, Unexplained Fever, Weight Gain, ARF, CHF, Pleuropericadial Effusions and Interstitial Pulmonary Infiltrates.
• Meticulous monitoring of Intake and Output. Daily weights
• Keep I/O matched (SHOULD BE Meticulous).
• Diuretics should be used if there is evidence of fluid retention and weight gain.
• Dexamethasone at 10 mg BID should be started as soon as symptoms are noted.
• In patients with a WBC >10,000, Dexamethasone 10 mg bid could be started before initiating ATRA
• Temporary discontinuation of ATRA or Arsenic Trioxide (ATO) is indicated only in case of severe APL DS.
**INDUCTION**

- **LOW RISK PATIENTS**
  - (WBC < 10,000 and Platelets > 40,000)
  - GIMEMA protocol. ATRA on Day 1 followed by Idarubicin 12 mg/m² on Days 2, 4, 6 and 8 (AIDA)

- **INTERMEDIATE RISK AND HIGH RISK PATIENTS**
  - (WBC > 10,000 and Platelet count < 40,000)
  - ATRA to be started as soon as diagnosis is suspected
  - Idarubicin to be started on the same day and given per the GIMEMA protocol on days 1, 3, 5 and 7. Even if the genetic results are not available, it is reasonable to give the Anthracycline

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**ARSENIC TRIOXIDE BASED INDUCTION**

Can be considered in the following patient groups

a) Low and intermediate risk patients (WBC < 10,000/ml)
b) Age > 70
c) Not candidates for conventional chemotherapy for any reason.
- Should be restricted to patients with confirmed PML-RAR alpha.
- ATRA at 45 mg/m² in divided doses twice a day along with
- Arsenic at 0.15 mg/kg daily, both continued till complete hematologic remission.
- Watch for differentiation syndrome.
- Follow for prolongation of QT interval. Keep Mg above 2.0 and K above 4.0.
- Follow LFTs and for grade 2 to 4 Liver Dysfunction, HOLD Arsenic.
**Algorithm**

**Work Up**
- CBC, CMP, and DIC Panel to include Fibrinogen, D-Dimers, PT and PTT twice a day until all laboratory and clinical coagulopathy is completely resolved.
- Echocardiogram.
- Bone Marrow Examination: Aspirate, Biopsy, Flow cytometry, Cytogenetics, FISH for PML-RAR alpha and PML-RAR alpha by PCR. Tumor banking is optional.
- Baseline Chest X-ray
- PICC Line. Do NOT attempt to put central lines or perform other surgically invasive procedures such as Bronchoscopy or Spinal Tap.
- Day 14 Marrow is not necessary.

**Supportive care**
- Tumor Lysis prophylaxis.
- Antibiotic Prophylaxis with Levofloxacin 500 mg po qd or similar antibiotic.
- Antifungal prophylaxis with Posaconazole 200 mg po tid, Voriconazole 200 mg po bid or another agent with similar efficacy.
- Anti-viral prophylaxis with Acyclovir 400 po bid or Valacyclovir 1000 mg PO daily.
- Red Cell transfusion is similar to other Leukemia Induction and suggested to transfuse at or below 7gm/dl.
- APL IS A MEDICAL EMERGENCY. TREATMENT WITH ATRA SHOULD BE STARTED ASAP.

**Coagulopathy**
- Intracranial, Pulmonary and GI Hemorrhage. Risk of Bleeding is worse in patients with Active Bleeding, Hypofibrinogenemia, Increased levels of D-Dimers, prolonged PT and PTT, increased WBC, increased Peripheral Blasts, Renal Failure and poor PS.
- Treatment with ATRA should start ASAP.
- Keep Platelets above 50,000.
- If there is clinical evidence of bleeding at presentation from needle sticks, Bone Marrow Biopsy sites, give 4 units of FFP as you are starting the ATRA and Chemotherapy. Continue FFP support twice a day until clinical bleeding resolves.
- Keep Fibrinogen above 150. Use Cryoprecipitate if needed.
- After all clinical and laboratory coagulopathy has resolved, the guidelines for blood product support are similar to management of other Leukemias.

**Differentiation Syndrome**
- Meticulous monitoring of Intake and Output.
- Daily weights
- Keep I/O matched (SHOULD BE METICULOUS).
- Diuretics should be used if clinically there is evidence of fluid retention and weight gain.
- Dexamethasone at 10 mg BID should be started as soon as symptoms are noted.
- In patients with a WBC >10,000, Dexamethasone 10 mg bid could be started before initiating ATRA.
- Temporary discontinuation of ATRA or Arsenic Trioxide (ATO) is indicated only in case of severe APL DS.
- Dexamethasone should be maintained until complete disappearance of symptoms and ATRA or ATO should be restarted. Dexamethasone should be stopped 3 days after all DS symptoms have resolved.

**Anthracycline based Induction**
- **INDUCTION OF LOW RISK PATIENTS** (WBC <10,000/ml and Platelets >40,000/ml)
  - GIMEMA protocol. ATRA on Day 1 followed by Idarubicin 12 mg/m2 on Days 2, 4, 6 and 8.
- **INDUCTION OF INTERMEDIATE RISK AND HIGH RISK PATIENTS** (WBC> 10,000 and Platelet count <40,000)
  - Idarubicin to be started on the same day and given per the GIMEMA protocol on days 1, 3, 5 and 7. Even if the genetic results are not available, it is reasonable to give the Anthracycline.
  - Aggressive management of coagulopathy.

**Arsenic trioxide based induction**
- Can be considered in the following patient groups
  - Low and intermediate risk patients (WBC < 10,000/ml)
  - Age >70
  - Not candidates for conventional chemotherapy for any reason.
- Should be commenced in patients with confirmed PML-RAR alpha.
- ATRA at 45 mg/m2 in divided doses twice a day, along with
  - Arsenic at 0.15 mg/kg daily, both continued till complete hematologic remission.
- Watch for differentiation syndrome.
- Follow for prolongation of QT interval. Keep Mg above 2.0 and K above 4.0.
- Follow LFTs and for grade 2 to 4 Liver Dysfunction, HOLD Arsenic.

**Hydroxyurea use for Leukocytosis:**
- NO LEUCOPHERESIS
- WBC 5 - 10k – Hydroxyurea 500 mg q day.
- WBC 10 – 15k Hydroxyurea 500mg BID
- WBC 15 – 20k – Hydroxyurea 500mg TID
- WBC 20 – 50k – Hydroxyurea 500 mg QID
- WBC > 50k – Hydroxyurea 1000 mg QID
- Could also give a dose or two of Idarubicin 12mg/m2 if the Leukocytosis does not resolve or DS does not resolve in spite of using Dexamethasone.

**Survival Pre and Post Algorithm**

![Survival Graph](image-url)
Patient Survival Pre and Post Algorithm
Experience in Other Diseases

- STEMI— Shorter door to balloon time improves survival
- In stroke patients administration of TPA within 3 to 4.5 hours of onset of symptoms improves survival
- **THE GOAL IS TO STREAMLINE THE PROCESS**

Funding

- Difficulty with obtaining funding - ECOG; CALGB
- American Society of Hematology (ASH)
- Lymphoma Leukemia Society (LLS) GRANT- $1.7 million (TAP)
- ACCC—Association of Community Cancer Centers
- ECOG Trial
- Survival in APL could improve from an estimated 65% to 90 + Percent - across the General population
Strategy to Decrease ED in this trial –
Main and Affiliate Sites

- Primary goal is to prospectively assess 30 day mortality; Secondary goal collect survival date
- Target the states of Georgia and South Carolina with a population of 15 million
- Widespread education of hematologists and oncologists about Early Deaths and the need for rapid diagnosis and treatment.
- At the Main Sites: Ad hoc meeting at patients’ admission with Physicians, Residents and nurses and rapid initiation of therapy
- At Affiliate sites: One of the Investigators will help manage the patients at the affiliate sites using the same algorithm as outlined in the strategy that we have used so far
- Accrual will be over 3 years – accrual goal 120 patients – decrease induction mortality to 5 - 8%
ECOG TRIAL and Associated Research

- D-Dimer levels and early indication of infection and DS
- CHF in APL
- DVT in APL
- FISH – 2 and 4 Hour FISH
- Micro RNA Arrays in APL
- Quality of Life
**EA9131- TRIAL DESIGN**

- **Suspected APL** (inclusion would be all APL patients)
  - Call ECOG Expert
  - Telephone consent
  - Review protocol (fax, email, website)

- **Treat locally with close follow-up**

**Planned coverage on new NCI-ECOG trial**

- Half the population of MN ~ 2.5m. Sub I: **Dr. Mark Litzow**
- Half of IL ~ 5 m, **Dr. Altman**
- Parts of NY and PA ~ 10 m, **Dr. Tallman**
- Parts of NC and TN ~ 8 m, **Dr. Luger**
- Cover entire population of ~ 15 million
- Half the population of FL ~ 10 million **Dr. James Foran**

States with Investigators: ECOG centers:
CONCLUSIONS

• Early Deaths can and **SHOULD** be prevented in APL.
• This concept has already been validated in Latin America- Brazil, Chile, Uruguay and Mexico. Decreased Early deaths from 32% to 15%. Rego et al.
• Expedite diagnosis and treatment
• Proactively manage the three main causes of death
• Treating oncologists may be unaware of the problem.
• This problem is not confined to “so called small and inexperienced centers”-- Inadequate supervision at larger treatment centers.
• Physician ego, apathy and unwillingness to seek advice.