Acute Promyelocytic Leukemia- Improving Survival in the Most Curable Leukemia; A Georgia and South Carolina Initiative.

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DISCLOSURES

• PI- Leukemia Lymphoma Society (LLS) – Grant for improving outcomes in APL.
• PI- Eastern Cooperative Oncology Group (ECOG/ACRIN) Trial- Decreasing Early Deaths in APL.
Leukemias and Outcomes

Chronic Leukemias

- **Chronic Myelogenous leukemia (CML)** – Multiple TKIs - 90+ % Survival
- **Chronic Lymphocytic Leukemia (CLL)** - Indolent disease in the elderly - Wide array of targeted treatments are available.

Acute Leukemias

- **Acute Lymphoblastic Leukemia (ALL)** - Generally Pediatric disease with 80% + cure rate.
- In Adults cure rates are approximately 50%
- **Acute Myelogenous Leukemia (AML)** - Seen generally in older patients.
- M1 to M7 - 50% cure rate across the spectrum
- **M3 – Acute Promyelocytic Leukemia (APL)**
APL Therapy: History

First description:
Hyperacute fatal illness associated with hemorrhagic syndrome

Discovery t(15;17) in APL

Daunorubicin in APL

In vivo leukemic cell differentiation

Differentiation of APL cells with RA

ATRA therapy

ATO in relapse

ATO frontline

ATRA + ATO ± GO


HIGHLY FATAL HIGHLY CURABLE

APL - Incidence

- APL is an uncommon disease with approximately 2000 new cases per year in the US.
- 16,000 practicing oncologists
- 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
APL Treatment and Outcomes
Large Trials
APL Survival in Large Cooperative Group Trials

Overall Survival

OS Probability

What Happens Outside a Trial?
### 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>Brazil (2007)</td>
<td>134</td>
<td>43</td>
<td>32%</td>
<td>66</td>
</tr>
<tr>
<td>Ankara &amp; Samsun Turkey (2010)(12)</td>
<td>49</td>
<td>20</td>
<td>40%</td>
<td>65</td>
</tr>
<tr>
<td>Swedish registry (2011)(6)</td>
<td>105</td>
<td>30</td>
<td>29%</td>
<td>41</td>
</tr>
<tr>
<td>SEER data(2011)(6)</td>
<td>1400</td>
<td>238</td>
<td>17%(24% in &gt;55yr)</td>
<td>Not discussed</td>
</tr>
<tr>
<td>AIIMS, India</td>
<td>33</td>
<td>6</td>
<td>18.1</td>
<td>58% in total patients during induction</td>
</tr>
<tr>
<td>Stanford (2012)(6)</td>
<td>70</td>
<td>19</td>
<td>26%</td>
<td>54</td>
</tr>
<tr>
<td>GRU (our 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, &gt;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>
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.

High Induction Mortality at GRU, AUGUSTA

- 19 patients were seen between 7/2005 and 6/2009
- 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 the first month have a > 90% chance of cure

Jillella et al, J Clin Oncol 30, 2012 (suppl; abstr 6573)
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
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 PATIENTS GET TRANSFERRED TO A MORE EXPERIENCED CENTER??
## 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 if available.
- 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.  Anti-Phosphorylase 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 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
- 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 until 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.d.
- **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.
Early Deaths Post Algorithm

Early Mortality of 7.1%.

10 deaths/141; 2 deaths censored
Patients managed by location

- **Georgia**
  - Augusta: 9 patients
  - Albany: 1 patient
  - Savannah: 3 + 1 patients
  - Pensacola: 2 + 3 patients
  - Clearwater: 1 patient

- **South Carolina**
  - Augusta: 6 patients
  - Columbia: 2 patients

- **Additional locations**
  - Birmingham: 1 patient
  - Montgomery: 1 patient
  - Charleston: 1 patient
  - Charlotte: 6 patients
  - Greenville: 2 + 3 patients

In addition:
- Phoenix: 2 patients
- Dallas: 1 patient
- Daytona: 1 patient
Funding

• Difficulty with obtaining funding - ECOG; CALGB
• American Society of Hematology (ASH)
• Lymphoma Leukemia Society (LLS) GRANT- $1.7 million (TAP)
• ECOG/ACRIN Trial (National Cancer Institute Trial)
• Survival in APL could improve from an estimated 65% to > 90 Percent - across the General population
Possible Reasons for Early Deaths

- Delay in diagnosis and treatment
- Suboptimal Supportive Care or non-availability?
- Treating oncologists may not be aware of the problem.
- Not confined to so called “inexperienced centers.” Also a problem at larger centers. Inadequate supervision at larger treatment centers by Leukemia Experts.
- Operator inexperience
- Apathy
- Physician Ego and Unwillingness to seek advice.
CONCLUSIONS

• Early Deaths can and **SHOULD** be prevented in APL.
• Model is to use the algorithm and communicate with an APL expert.
• Helped Create Awareness- most pressing problem 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.
• The GA and SC trial- based on our preliminary results will improve population wide survival.
• Study has been implemented through the GACORE Network
• The National ECOG/ACRIN Trial will start accrual soon.