PHASE II TRIAL OF AZACITIDINE PLUS DEFERASIROX IN HIGHER RISK MYELO DysPLASTIC SYNDROMES (MDS)

Anca Prica MD, FRCPC
Hematology/Oncology fellow
Sunnybrook Hospital/Odette Cancer Centre, Toronto
Supervisors/Co-Investigators: Dr. Rena Buckstein and Dr. Richard Wells
## Disclosures for Anca Prica

<table>
<thead>
<tr>
<th>Employment</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consultancy</td>
<td>None</td>
</tr>
<tr>
<td>Equity Ownership</td>
<td>None</td>
</tr>
<tr>
<td>Research Funding</td>
<td>None</td>
</tr>
<tr>
<td>Honoraria</td>
<td>None</td>
</tr>
<tr>
<td>Patents &amp; Royalties</td>
<td>None</td>
</tr>
<tr>
<td>Speakers Bureau</td>
<td>None</td>
</tr>
<tr>
<td>Membership on Board of Directors/Advisory Committee</td>
<td>None</td>
</tr>
<tr>
<td>Other</td>
<td>None</td>
</tr>
<tr>
<td>Presentation includes a description of the following off-label use of a drug or medical device</td>
<td>Deferasirox</td>
</tr>
</tbody>
</table>
**BACKGROUND**

- In MDS – low blood counts including red blood cells leading to anemia

- 2 risk groups: lower and higher

Higher risk patients:
- More symptoms, need more support with transfusions
- Increased risk of becoming AML
- Shorter life expectancy
STANDARD TREATMENT FOR HIGHER RISK MDS

Azacitidine (Vidaza)
- Large study on patients with higher-risk MDS showed that patients:
  - Lived longer (about 9 mo longer)
  - Less likely to need transfusions or antibiotics
  - Had an improved quality of life
- However, a large proportion of people still don’t respond to the drug or remain transfusion dependant
- Other treatments are needed
Transfusions and Iron Overload

- 70% of higher risk patients are transfusion dependant
- Average iron absorption is 1–2 mg/day through gut
- 1 blood unit contains 200-250 mg iron
- Iron overload can occur after 10–20 transfusions
- Measured in the blood as ferritin
Iron Loading

Iron Overload

Formation of reactive iron in the blood

Uncontrolled iron loading of organs:
- Pituitary
- Thyroid
- Heart
- Liver
- Pancreas
- Genitals
CHELATION

- The body cannot remove excess iron on its own
- Chelators are drugs that allow removal of body iron
- Two drugs licensed in Canada
  - desferoxamine (Desferal) given as an infusion overnight
  - deferasirox (Exjade) given orally – newer drug
- have been shown to decrease iron in the blood, but unclear if makes people live longer in MDS (small studies)
- Only studied in lower risk MDS
BAD EFFECTS OF IRON LOADING

Worse survival if ferritin >1000

Better survival with chelation

Sanz et al., Blood 2008 112 (abstract 640)

Rose et al, Leuk Res. 2010. 34(7):864-870
IRON OVERLOAD MAY BE ASSOCIATED WITH INCREASED LEUKEMIA

Dr. Wells and his team have shown progression to leukemia in iron overloaded mice.
IRON CHELATION IMPROVES ANEMIA

- Large trial evaluation of Exjade
- Subset of lower risk MDS patients
- 23% of patients had a response in their red blood cell counts
- Mechanism – reversal of toxic effects of iron on bone marrow stem cells
PHASE II TRIAL OF AZACITIDINE PLUS DEFERASIROX IN HIGHER RISK MYELODYSPLASTIC SYNDROMES (MDS)
Clinical trial objectives

- **Primary**
  - Determine proportion of patients with blood count improvement with the addition of Exjade to Vidaza

- **Secondary**
  - Determine safety of Exjade + Vidaza
  - Assess
    - markers of iron overload such as reactive iron in the bone marrow
ELIGIBILITY

- **Inclusion**
  - Adults >18 yrs of age
  - Higher risk MDS
  - Vidaza X 6 cycles with no blood count improvement, but stable disease as per IWG criteria
  - Ferritin >500

- **Exclusion**
  - Kidney abnormalities
  - Liver abnormalities
TREATMENT PLAN

- Continue Vidaza
- Half the patients: Add Exjade for 6 months
- Half the patients: Continue azacitidine alone for an extra 6 months
- Dose changes as needed
- At study end
  - Stop Exjade
  - Continue Vidaza
**Response Assessment**

- **IWG criteria:**

<table>
<thead>
<tr>
<th>Response Type</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red blood cell response</td>
<td>Increase in red blood cell count by 15 or ≥4 transfusions/8wks</td>
</tr>
<tr>
<td>Platelet response</td>
<td>↑ by 30 if &gt;20 at start or 100% if 10 to &gt;20</td>
</tr>
<tr>
<td>Neutrophil response</td>
<td>≥ 100% and absolute &gt; 0.5</td>
</tr>
<tr>
<td>Stable disease</td>
<td>Bone marrow evaluation – no progression</td>
</tr>
</tbody>
</table>

- Bloodwork weekly for the first 8 weeks, then every 2 weeks until study completion.
- BM at study entry, half way through at 3 months and at study completion or patient withdrawal.
- Side effects monitored every month.
Start Here

Informed Consent

Screening

Randomization

Vidaza + Exjade
6 months
55 patients

6 months post treatment follow up

Vidaza alone
6 months
55 patients

6 months post treatment follow up
WHERE?

- 1st stage:
- 26 patients (half in each group)
- At Sunnybrook Hospital/Odette Cancer Centre
- If responses, would expand to multiple centres through Canada
STATUS

- Still in the planning stages
- Working on the final approval for the protocol
- Hope to start enrolling in about 6-9 months
THANK YOU

- AAMAC – providing funds for fellowship award and to help complete this research
- CIHR
- Dr. Buckstein and Dr. Wells
- Novartis Oncology
- In advance, you, the patients