GIST Day of Learning
March 10, 2018
Scottsdale, Arizona
March 10th, 2018

ABOUT GDOL

GDOL is a free one day event to help patients and caregivers learn more about this rare cancer, find support, and enhance their knowledge base to help them navigate their cancer journey.

The Life Raft Group has a simple focus: to cure a form of cancer — GIST — and to help those living with it until then. To do this, the Life Raft Group focuses on three key areas: research, patient support & education, and advocacy, which lay the foundation of our mission to ensure the survival of GIST patients through a comprehensive approach connecting individual patients’ needs, the worldwide community of GIST advocates and the global health and research environment.

LOCATION

Mayo Clinic
Taylor Auditorium
13400 E. Shea Blvd.
Scottsdale, AZ 85259
The many faces of gastrointestinal stromal tumor
Overview

- GIST background and molecular biology
- Symptomatology
- Diagnosis
- Treatment options
  - Localized disease
  - Metastatic disease
  - Recurrent disease
There is new ammunition in the war against cancer. These are the bullets.

Revolutionary new pills like GLEEVEC combat cancer by targeting only the diseased cells. Is this the breakthrough we’ve been waiting for?
What are gastrointestinal stromal tumors?

- Sarcoma of digestive supportive tissue
- Birth year: 2000
- Rare: 10/million, 4K-6K/yr (US)
- Average age: 50 yrs, M>W
- Arise from pacemaker cells of the digestive tract (Interstitial cells of Cajal)
- CD117 (KIT) expression
- Genetic factors can increase risk of GIST (Neurofibromatosis-1, carney triad)
GISTs can happen anywhere in the digestive tract

- 70%
- 20-25%
- 5-10%
GIST Timeline

1983: First described by Mazur and Clark[1]
1995: CD34 identified as a relatively specific marker[2]; similarities between GIST cells and interstitial cells of Cajal
1998: 2 major discoveries[3]:
  - KIT staining 94% of GIST
  - Activating mutations in KIT gene (5 out of 6)
2006: Accelerated FDA approval of sunitinib as second-line therapy
2013: FDA approval of regorafenib as third-line therapy

What symptoms could be expected?

- Abdominal pain/pressure
- Nausea
- Bleeding
- Anemia
- Fatigue
- Intestinal obstruction
How is it diagnosed?

- Blood test...anemia, iron deficiency, but no cancer marker
- CT scan (*choi criteria)
- MRI scan
- PET/CT scan
- Endoscopic ultrasound (EUS)
- Endoscopy (EGD, colonoscopy)
- Biopsy: KIT and DOG-1 staining, mutation testing for KIT/PDGFR, SDH
Can my cancer spread?

- 1 in 5 can have metastatic disease at diagnosis
- Sites: abdominal cavity, liver, peritoneum
- Spread to lung, bone or brain is RARE
- Lymph node spread is more common in pediatric GISTs, pediatric type GIST in young adults.
What determines outcome?

- Size of tumor
- Location (stomach vs. others)
- Mitotic rate (high vs. low)
- **Molecular/Mutation status**
  - KIT vs. PDGFR
  - Wild type vs. SDH deficient

*Figure 1 “You’ve got something unaffordable.”
Note: Courtesy of Banx Cartoons/Financial Times, Thursday September 24, 2015, page 12, with permission.*
**Mutation, mutation, mutation**

**KIT**

- (~ 85% GISTs)
- Exon 9 (18.1%)
- Exon 11 (66.9%)
- Exon 13 (1.6%)
- Exon 17 (1.6%)

**PDGFRA**

- (~ 5% to 7%)
- Exon 12 (0.8%)
- Exon 18 (3.9%)

**Wild Type**

- (10% to 15 %)
  - BRAF mutation (V600E exon 15)
  - IGF-1R
  - Succinate Dehydrogenase
  - Alternate mutations (AKT/PTEN/TRK)

**Membrane**

**Cytoplasm**

---


Slide credit: clinicaloptions.com
Why is mutation so important?

- Determine choice and dose of treatment
  - Neoadjuvant
  - Adjuvant
- Understand risk for family members
- Clinical trials
How long do I have to live?

- General survival rates (@ 5 yrs): NCI database
  - Localized disease: 91%
  - Locally advanced: 74%
  - Metastatic disease: 48%
Is my cancer treatable and curable?

- Depends on the stage, resectable vs. unresectable, risk category of disease
  - Operable: surgery (Dr. Wasif)
    - Low risk: no additional therapy after surgery
    - Intermediate or high risk: “adjuvant therapy” x 3 yrs after surgery
  - Locally advanced and not amenable to upfront surgery: medical treatment (such as Gleevec) before surgery
<table>
<thead>
<tr>
<th>Mitotic Index</th>
<th>Size</th>
<th>Gastric (n=1055)</th>
<th>Jejunum/Ileum (n=629)</th>
<th>Duodenum (n=144)</th>
<th>Rectum (n=111)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤5 per 5 mm²</td>
<td>≤ 2 cm</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>&gt; 2 ≤ 5 cm</td>
<td>1.9%</td>
<td>4.3%</td>
<td>8.3%</td>
<td>8.5%</td>
</tr>
<tr>
<td></td>
<td>&gt; 5 ≤ 10 cm</td>
<td>3.6%</td>
<td>24%</td>
<td>Insuff. data</td>
<td>Insuff. data</td>
</tr>
<tr>
<td></td>
<td>&gt; 10 cm</td>
<td>10%</td>
<td>52%</td>
<td>34%</td>
<td>57%</td>
</tr>
<tr>
<td>&gt;5 per 5 mm²</td>
<td>≤ 2 cm</td>
<td>(None)</td>
<td>(High)</td>
<td>Insuff. data</td>
<td>54%</td>
</tr>
<tr>
<td></td>
<td>&gt; 2 ≤ 5 cm</td>
<td>16%</td>
<td>73%</td>
<td>50%</td>
<td>52%</td>
</tr>
<tr>
<td></td>
<td>&gt; 5 ≤ 10 cm</td>
<td>55%</td>
<td>85%</td>
<td>Insuff. data</td>
<td>Insuff. data</td>
</tr>
<tr>
<td></td>
<td>&gt; 10 cm</td>
<td>86%</td>
<td>90%</td>
<td>86%</td>
<td>71%</td>
</tr>
</tbody>
</table>

Miettinen & Lasota, Semin Diagn Pathol, 23(2):70-83, 2006
Do I need chemotherapy?...NO
## Chemotherapy Trials

### Advanced GIST

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Number of Patients</th>
<th>Partial Response n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOX + DTIC</td>
<td>43</td>
<td>3 (7%)</td>
</tr>
<tr>
<td>DOX + DTIC +/- IF</td>
<td>60</td>
<td>10 (15%)</td>
</tr>
<tr>
<td>IF + VP-16</td>
<td>10</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>15</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>17</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Liposomal DOX</td>
<td>15</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>DOX</td>
<td>12</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>DOX or docetaxel</td>
<td>9</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>High-dose IF</td>
<td>26</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>EPI + IF</td>
<td>13</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Various</td>
<td>40</td>
<td>4 (10%)</td>
</tr>
<tr>
<td>DTIC/MMC/DOX/CDDP/GM–CSF</td>
<td>21</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Temozolamide</td>
<td>19</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>280</strong></td>
<td><strong>19 (6.8%)</strong></td>
</tr>
</tbody>
</table>
What are the approved treatment options?

- Imatinib (Gleevec)
- Sunitinib (Sutent)
- Regorafenib (Stivarga)
GIST molecular landscape has become very complicated

- KIT Exon 11: 66%
- KIT Exon 9: 9%
- KIT Exon 13: 2%
- KIT Exon 17: 1%
- PDGFRA Exon 12: 2%
- PDGFRA Exon 14: 0%
- PDGFRA Exon 18 (other): 2%
- PDGFRA Exon 18 D842V: 7%
- SDHA/B/C/D mutation: 6%
- SDHC methylation: 2%
- BRAF: 2%
- RAS: 0.10%
- NF1: 1%
What are my chances of responding to treatment?

~ 20% of pts have unresectable/metastatic disease; > 40% of resected tumors recur and metastasize

- **Pre-imatinib**
  - Localized disease: 5-yr OS < 50%
  - Metastatic GIST median OS: 5-12 mos

- **With targeted therapy (post-2001)**
  - Localized disease 5-yr OS: > 80%
  - Metastatic GIST median OS: ≥ 60 mos (pre-sunitinib/regorafenib < 60 mos)
  - No difference between 400mg once vs. twice daily
What happens when imatinib stops working?

- Nearly one half of pts develop resistance to initial imatinib/targeted therapy within 2 yrs
- Primary resistance (within 6 mos, 10% to 15%)
  - KIT exon 17, PDGFR exon 18 mutations, BRAF, KRAS
- Secondary resistance
  - Acquired secondary mutations: usually in tumors with exon 11 primary mutation
  - Activation of alternate drivers/pathways: PI3K/AKT/mTOR, IGFR1
### How effective are Sunitinib and Regorafenib?

<table>
<thead>
<tr>
<th>Name of study</th>
<th>Setting</th>
<th>N</th>
<th>Randomized arms</th>
<th>PFS/RFS</th>
<th>OS</th>
<th>Response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACOSOG Z9001 (41)</td>
<td>Adjuvant</td>
<td>713</td>
<td>1-year imatinib vs. placebo</td>
<td>1-year RFS 98% vs. 83% (P&lt;0.0001)</td>
<td>HR =0.816; P=0.438</td>
<td>Not available</td>
</tr>
<tr>
<td>SSG XVIII/AIO (29)</td>
<td>Adjuvant</td>
<td>400</td>
<td>1- vs. 3-year imatinib</td>
<td>5-year RFS 66% vs. 48% (P&lt;0.0001)</td>
<td>5-year OS 92% vs. 82% (P=0.02)</td>
<td>Not available</td>
</tr>
<tr>
<td>EORTC (52)</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; line metastatic</td>
<td>946</td>
<td>400 vs. 800 mg imatinib</td>
<td>2-year PFS 56% vs. 50% (P=0.026)</td>
<td>2-year OS 69% vs. 74%</td>
<td>50% vs. 54%</td>
</tr>
<tr>
<td>North American Sarcoma Intergroup study (S0033) (53)</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; line metastatic</td>
<td>746</td>
<td>400 vs. 800 mg imatinib</td>
<td>2-year PFS 50% vs. 53%</td>
<td>2-year OS 73% vs. 78%</td>
<td>43% vs. 41%</td>
</tr>
<tr>
<td>Demetri &lt;i&gt;et al.&lt;/i&gt; (63)</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; line metastatic</td>
<td>243</td>
<td>Sunitinib vs. placebo</td>
<td>Median 27.3 vs. 6.4 weeks (P&lt;0.0001)</td>
<td>Median 72.7 vs. 64.9 weeks (P=0.306)</td>
<td>Not available</td>
</tr>
<tr>
<td>GRID (72)</td>
<td>3&lt;sup&gt;rd&lt;/sup&gt; line metastatic</td>
<td>199</td>
<td>Regorafenib vs. placebo</td>
<td>Median 4.8 vs. 0.9 months (P&lt;0.0001)</td>
<td>Same (HR =0.77; P=0.199)</td>
<td>76% vs. 35%</td>
</tr>
</tbody>
</table>

GIST, gastrointestinal stromal tumors; RFS, recurrence-free survival; OS, overall survival; HR, hazard ratio.
What is known about SDH deficient and Wild type GIST?

- Common in younger patients
- W>M
- Absent KIT/PDGFR mutation
- Gastric GISTs, multilobular, multiple
- Poor response to Imatinib
- Proven responses to Sunitinib, Regorafenib
- Novel therapies: targeting HIF, VEGF pathways
- Local therapies: surgery, RFA/Embolization
GIST Treatment Algorithm

Newly Diagnosed GIST
- Staging (CT/MRI or PET/CT)
- Molecular testing for mutations

Localized GIST
- Assess if reducing tumor bulk improves chance of organ preservation or R0 resection AND no resistant mutation?
  - No
    - Surgery
      - Assess risk for recurrence (size/mitotic rate/location/rupture)
  - Yes
    - Neoadjuvant Imatinib
      - 400 mg/day
      - Continue till maximum reduction in size or when R0 surgery becomes feasible

Adjuvant Imatinib
- 400 mg/day for at least 3 yrs in high-risk pts

Surgery
- Adjuvant imatinib for high-risk pts (based on pre-imatinib risk assessment)

Consider Surgery
- If all visible residual tumor can be removed or for focal progression
  - Continue TKI

Advanced/Metastatic
- Imatinib 400 mg/day
  - Increase to 800 mg/day if exon 9 KIT mutation

Responding to Imatinib/TKI
(Continue long-term)

Progression on Imatinib/TKI
- Primary or secondary resistance
  - Yes
    - Consider Surgery
      - If all visible residual tumor can be removed or for focal progression
      - Continue TKI
    - Consider Localized Liver-Directed Therapy
      - Embolization/RFA
      - Continue TKI
  - No
    - Options
      - Imatinib 800 mg/day
      - Sunitinib
      - Regorafenib
      - Clinical trials (consider early for PDGFR D842V mutation)
Summary

- GISTs are very heterogeneous
- Understand the molecular/mutational abnormality
- Adjuvant imatinib improves progression free and overall survival
- Resistance to tyrosine kinase inhibitors is a problem
- Newer drugs in clinical trials will likely improve outcomes
- Need better understanding and treatments for wild type and SDH deficient GIST
THANK YOU!