Overview of GIST and its Medical Management (i.e. GIST 101)

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OVERVIEW

• What is GIST?
• How do we treat GIST?
• How do we use imatinib (Gleevec) in GIST?
• What are the options for imatinib-resistant GIST?
• How do we manage side effects of imatinib?
What is GIST?

- Gastrointestinal stromal tumor, the most common type of sarcoma
- A tumor of the interstitial cells of Cajal (ICC)
- Can occur at any point in the digestive organs, including stomach (most common), small intestine, large intestine, and rectum
Why do GISTs grow?

- 80% of GISTs have a mistake (mutation) in the genetic code that results in a hyperactive KIT protein (light-switch ON)

- We recommend that patients have their tumor mapped (called sequencing) to determine which exon has the mutation

- Up to 20% of GISTs may have a mistake in a NON-KIT gene – important for treatment!!! (more later)
Who gets GIST?

- Overall, only about 5000 new GISTs per year
- Most common in 40-60 year old patients, similar rates in men and women
- Gastrointestinal symptoms of GIST include pain, nausea, lack of appetite, bleeding.
- Incidental findings in endoscopy
- Very rarely, a special type of GIST can be passed down in families or occur in children
- No known risk factors
How do we treat GIST?

- LOCAL vs. SYSTEMIC treatment
- Surgery is the goal! (Complete removal of the GIST)
- GISTs are relatively resistant to radiation
- Metastases – spread of the tumor cells to the liver, or inside the abdomen (peritoneal disease), less common to lung, bone, etc.
- Most recurrences happen within 2 years of the surgery
Risk determination in GIST

• How likely is it that the GIST will come back after removal by surgery?
• GISTs are classified into \textbf{LOW risk}, \textbf{INTERMEDIATE risk}, and \textbf{HIGH risk} based on:
  • \textbf{Size} (less than 5 cm, 5-10 cm, or greater than 10 cm)
  • \textbf{Location} (gastric vs other sites)
  • \textbf{Mitoses} (a measure of the speed of growth in the cells)

Estimated chance of recurrence/metastasis:

<table>
<thead>
<tr>
<th>Location (GASTRIC vs OTHER)</th>
<th>GASTRIC (stomach)</th>
<th>OTHER (intestine, etc)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5 cm</td>
<td>&lt; 5% &lt; 5%</td>
<td>12-15% &lt; 5%</td>
</tr>
<tr>
<td>5-10 cm</td>
<td>&lt; 5% &lt; 5%</td>
<td>49-86% 25%</td>
</tr>
<tr>
<td>&gt; 10 cm</td>
<td>12-15% 49-86%</td>
<td>30-60% 70-90%</td>
</tr>
</tbody>
</table>

Adapted from NCCN guidelines, from Miettinen M, Lasota J. Sem Diagn Pathol 2006.
Uses of systemic treatment in GIST

- To **prevent** the recurrence or metastasis after surgery in high-risk GIST patients

- To **shrink** a GIST tumor that cannot be removed completely by surgery at the time it is found. (it is in a bad spot…)

- To **control** GIST that has already spread to other organs or inside of the abdominal cavity (peritoneal disease)
# Systemic treatment in GIST

**Old-school chemotherapy in advanced GIST**

<table>
<thead>
<tr>
<th>Regimen</th>
<th># Patients</th>
<th>% Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOX + DTIC</td>
<td>43</td>
<td>7%</td>
</tr>
<tr>
<td>DOX + DTIC +/- IF</td>
<td>60</td>
<td>15%</td>
</tr>
<tr>
<td>IF + VP-16</td>
<td>10</td>
<td>0%</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>15</td>
<td>7%</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>17</td>
<td>0%</td>
</tr>
<tr>
<td>Liposomal DOX</td>
<td>15</td>
<td>0%</td>
</tr>
<tr>
<td>DOX</td>
<td>12</td>
<td>0%</td>
</tr>
<tr>
<td>DOX or docetaxel</td>
<td>9</td>
<td>0%</td>
</tr>
<tr>
<td>High-dose IF</td>
<td>26</td>
<td>0%</td>
</tr>
<tr>
<td>EPI + IF</td>
<td>13</td>
<td>0%</td>
</tr>
<tr>
<td>Various</td>
<td>40</td>
<td>10%</td>
</tr>
<tr>
<td>DTIC/MMC/DOX/CDDP/GM–CSF</td>
<td>21</td>
<td>5%</td>
</tr>
<tr>
<td>Temozolamide</td>
<td>19</td>
<td>0%</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>280</strong></td>
<td><strong>6.8%</strong></td>
</tr>
</tbody>
</table>
The role of imatinib in GIST

- Imatinib is an oral chemotherapy drug
- Binds to the ATP-binding site and blocks the downstream signaling to the cell from hyperactive KIT
- Works best in exon 11 mutated GIST, other mutation sites tend to be more resistant
GIST Subtypes

- Kit mutation ~80% of GISTs
  - Exon 11 (~70%): codon 557-558 (risky)
  - Exon 9 (~10%)
  - Exon 13/14 (~1%) resistant
  - Exon 17 (<1%) resistant

- PDGFR mutation ~10% of GISTs
  - Exon 12
  - Exon 18 D842V (resistant)

- SDH-B deficient
- Raf V600E
- NF-1
- Ras
- PI3K
- IGF-1R overexpressed
- TRK fusion
- “wild-type”
The First GIST Patient: Histology

H&E (at diagnosis)

H&E

Ki 67

CD117

Pretreatment

One month of therapy

CT response in GIST
Marked Biologic Response Revealed by PET Scan

Multiple liver and upper abdominal $^{18}$FDG-accumulating metastases

A marked decrease in $^{18}$FDG uptake 4 weeks after starting imatinib mesylate

“Pseudoprogression” in GIST
How do we treat GIST?

- Adjuvant therapy with imatinib
  - Use after surgery to prevent the GIST from coming back when there is NO visible evidence of remaining tumor.
  - Routinely recommended for high risk patients, and many intermediate risk patients
  - Optimal length of treatment still under investigation…
Adjuvant therapy

- 1-year RFS 98% - Imatinib 400 mg
- 1-year RFS 80% - Placebo
- Recurrence in imatinib arm increases at 18 months (6 months following discontinuation of therapy)

- RFS was significantly improved in Imatinib arm in each tumor size category but greatest for tumors > 10 cm

(DeMatteo et al, 2009)
How long should we continue imatinib?

• Prospective, open-label, phase III trial
• 400 patients with operable primary GIST
  • >5cm, >5 mitoses/50 HPF
• Based on this study, standard duration is three years, but ongoing trial is investigating five year treatment (PERSIST5).
• At 3 year mark, only 4 / 91 patients have recurred (1 with resistant mutation, 3 after discontinuing imatinib.)
• Maybe longer…?

<table>
<thead>
<tr>
<th></th>
<th>36 months</th>
<th>12 months</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib (400mg/day)</td>
<td>N = 200</td>
<td>N = 200</td>
<td></td>
</tr>
<tr>
<td>5-year RFS</td>
<td>Imatinib 66%</td>
<td>Imatinib 48%</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>5-year OS</td>
<td>Imatinib 92%</td>
<td>Imatinib 82%</td>
<td>P = 0.019</td>
</tr>
</tbody>
</table>

SSG XVIII, Joensuu H et al. ASCO 2011, ASCO 2015 abstract 10537, Raut et al.
How do we treat GIST?

Neo-adjuvant therapy with imatinib

- Shrink/liquefy GIST tumors so complete resection with surgery is possible
- Consider for
  - Unresectable/borderline resectable tumors
  - Tumors requiring extensive resection of involved organs
  - Potentially resectable metastatic GIST
- Controversial – multidisciplinary evaluation required

Important steps –
- sequencing to determine mutation - Is it likely to respond to imatinib?
- Get accurate imaging at baseline, including a PET, as PET may show response to treatment even if size doesn’t change.
### Neoadjuvant imatinib

**RTOG 0132-ACRIN 6665**

63 patients

<table>
<thead>
<tr>
<th>Group A, localized (n=30)</th>
<th>Group B, metastatic (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response</strong></td>
<td></td>
</tr>
<tr>
<td>7% PR, 83% SD, 10% unk</td>
<td>4.5% PR, 91% SD, PD 4.5%</td>
</tr>
<tr>
<td><strong>Estimated 2-year PFS</strong></td>
<td></td>
</tr>
<tr>
<td>82.7%</td>
<td>77.3%</td>
</tr>
<tr>
<td><strong>Estimated 5-year PFS</strong></td>
<td></td>
</tr>
<tr>
<td>57%</td>
<td>30%</td>
</tr>
<tr>
<td><strong>Estimated 2-year OS</strong></td>
<td></td>
</tr>
<tr>
<td>93.3%</td>
<td>90.9%</td>
</tr>
<tr>
<td><strong>Estimated 5-year OS</strong></td>
<td></td>
</tr>
<tr>
<td>77%</td>
<td>68%</td>
</tr>
<tr>
<td><strong>Type of Resection</strong></td>
<td></td>
</tr>
<tr>
<td>R0</td>
<td>77%</td>
</tr>
<tr>
<td>R1</td>
<td>15%</td>
</tr>
<tr>
<td>R2</td>
<td>8%</td>
</tr>
<tr>
<td>Unspecified</td>
<td>5%</td>
</tr>
</tbody>
</table>

**RTOG 0132 Schema**

- Kit positive locally advanced or metastatic/recurrent GIST (Group A primary ≥ 5cm), (Group B metastatic ≥ 2cm)
- Pre-operative Imatinib 600 mg/d for 8 to 12 weeks
- SD/PR → Resection → continued Imatinib 600 mg/d for 2 yrs.
- F/U for 1st PFS
- 2nd RR
- Toxicity
- OS
- Physicians option (off study)
How do we treat GIST?

**Treatment of metastatic disease with imatinib**

- Goal is to neutralize the existing tumor and prolong the time to progression

- Progression on a treatment occurs when some of the cells in the tumor develop resistance to the drug, and begin growing (can be regrowth of a previous tumor, or the development of a new tumor)

- Most commonly, the resistant cells that remain have a different or additional mutation that makes them resistant to the imatinib

- Sometimes this can be overcome by increasing the imatinib dose
Imatinib for metastatic/unresectable GIST

- Combined data from two large trials (1640 patients) with metastatic or advanced GIST
- Treated with imatinib at either 400 mg or 800 mg
- Median time to progression 1.58 yrs on the 400 mg arm, 1.95 yrs on the 800 mg arm, 30-35% free from progression at 3 years
- Significant benefit to 800 mg only in exon 9 patients

LENGTH OF TREATMENT IN METASTATIC GIST

- Ok, my GIST now has shrunk or stabilized – how long do I need to stay on imatinib?
- Can I take a break from imatinib or will my tumors start to grow again?
- Does staying on imatinib longer help prevent the GIST from developing resistance?
Advanced/metastatic GIST
434 patients

RANDOMISATION

Imatinib for 1 year

Imatinib for 3 years

Imatinib for 5 years

71 patients without progression

Imatinib 400 mg

PD

STOP

Imatinib 400 mg
Patients who progressed were restarted on imatinib, and 94% of patients had tumors respond again to imatinib.

BUT – in patients who got CR initially, only 41.7% achieved it again with rechallenge, and in patients with PR, only 56% were able to achieve it again. Development of resistance?

Our practice – DON’T STOP!

<table>
<thead>
<tr>
<th></th>
<th>Continued imatinib</th>
<th>Stopped imatinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib 1 year</td>
<td>8/26 PD</td>
<td>26/32 PD</td>
</tr>
<tr>
<td></td>
<td>PFS 18 mos</td>
<td>PFS 6.1 mos</td>
</tr>
<tr>
<td>Imatinib 3 year</td>
<td>7/25 PD</td>
<td>21/25 PD</td>
</tr>
<tr>
<td></td>
<td>1 yr PFS 92%</td>
<td>1 yr PFS 32%</td>
</tr>
<tr>
<td>Imatinib 5 year</td>
<td>0/10 PD (at 1 year)</td>
<td>5/11 PD (at 1 year)</td>
</tr>
</tbody>
</table>
Putting it all together… so far?

- Intermediate and high risk GISTs are likely to leak cells out into the abdomen which can lead to recurrence and metastasis, even if the initial tumor is completely removed.

- The use of imatinib can result in rapid, dramatic tumor shrinkage, and is often underappreciated with traditional CT scans.

- If possible, surgical removal of tumors appears to improve the outcome, even if the GIST has already spread. Multidisciplinary evaluation with sarcoma surgeons is critical.

- Imatinib can control the growth of resistant cells for years, but when stopped, these cells often begin growing again.

- Unfortunately, most GIST tumors ultimately will progress despite imatinib therapy and we require new drugs that are effective against imatinib-resistant cells.

- Until we have new drugs that can KILL all of the GIST cells up front, the best defense is to use imatinib as a maintenance medication as long as possible for high-risk or metastatic tumors.
Type of Progression

- Stable disease
  - Stable lesion
  - Progressing lesion
- Limited progression
- Nodular progression
- Widespread progression
Secondary mutations

KIT:

Extracellular Domain (exon 9, 10.2%)

Juxtamembrane Domain (exon 11, 66.1%)

Tyrosine Kinase Domain I (exon 13/14, 1.2%)

Tyrosine Kinase Domain II (exon 17, 0.6%)

Imatinib

Options if imatinib-resistant

- Limited or Nodular Progression
  - Ablations (chemo, freeze, burn, electrocute…)
  - Surgical Resection
  - Radiation (including stereotactic - Cyberknife)

- Widespread progression
  - Consider sequencing or re-biopsy
  - Increase Imatinib to 800 mg daily
  - Sunitinib, Regorafenib
  - Clinical trial
  - Other tyrosine kinase inhibitors

Phase III Trial: US Intergroup S0033

TIME TO TUMOR PROGRESSION

Progression-free Survival
Comparison of Central Review vs Investigator Assessments


PFS 4.8 vs 0.9 months (p<0.0001)
## Other Agents for Imatinib-Resistant GIST

<table>
<thead>
<tr>
<th>CLASS</th>
<th>AGENT</th>
<th>TRIAL PHASE</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>KIT Inhibitors</td>
<td>Sorafenib</td>
<td>II</td>
<td>PR=13%, SD=58% PFS=5 months</td>
</tr>
<tr>
<td></td>
<td>Dasatinib</td>
<td>II</td>
<td>PR=22%, SD=24% PFS=2 months</td>
</tr>
<tr>
<td></td>
<td>Nilotinib</td>
<td>I/II/III</td>
<td>PR=10%, SD=37% PFS=3 months</td>
</tr>
<tr>
<td></td>
<td>Pazopanib</td>
<td>II</td>
<td>SD=48% PFS=1.9 months SDH-17 cycles</td>
</tr>
<tr>
<td></td>
<td>Axitinib</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>PDGFR inhibitors (D842V)</td>
<td>Crenolanib, BLU-285</td>
<td>III, I</td>
<td>CBR 31%, 56% PFS&gt;6 months</td>
</tr>
<tr>
<td>Raf Inhibitors</td>
<td>Vemurafenib</td>
<td>I</td>
<td>ND</td>
</tr>
<tr>
<td>mTOR Inhibitors</td>
<td>Everolimus</td>
<td>II/III</td>
<td>PR=2%, SD=43% PFS=3.5 months</td>
</tr>
<tr>
<td>PI3K Inhibitors</td>
<td>Buparlisib (BKM120)</td>
<td>I/II</td>
<td>Recruiting</td>
</tr>
<tr>
<td>HDAC inhibitors</td>
<td>Vorinostat</td>
<td>NA</td>
<td>ND</td>
</tr>
<tr>
<td>Placebo</td>
<td>Various</td>
<td>III</td>
<td>PR=0% PFS=1- 1.5 months</td>
</tr>
</tbody>
</table>

HDAC=histone deacetylase; IGF-1R=insulin-like growth factor–1 receptor; MKI=multitargeted kinase inhibitor; mTOR=mammalian target of rapamycin.
Life with imatinib

- **Tyrosine kinase inhibitors**
  - Block RECEPTORS on the surface of cells
  - Dirty drugs
  - The idea is that a particular receptor and its chain-of-command are MORE active in the cancer cell compared to a normal cell – but all cells have these receptors
  - Thus, while killing the cancer, non-cancer cells will also experience disruptions in their normal way of life = side effects (on-target effects)
Drug interactions

- Imatinib is meant to be taken with food and water – (taking on an empty stomach leads to LESS exposure to the active drug, or undertreatment!)

- Prohibited medications and juices/supplements (lead to increased levels of imatinib with worse side effects)
  - St. Johns Wort
  - Grapefruit juice
  - Star fruit, pomegranate juice
  - Coumadin
  - Can increase levels of cholesterol and blood pressure medications - check with your doctor
  - Tylenol, alcohol – stresses the liver
  - Iron supplements, changes absorption
Most common side effects

- Swelling/fluid retention, often around the eyes
- Nausea/vomiting/abdominal discomfort
- Loss of appetite
- Fatigue
- Muscle/bone/joint aches and pains
- Diarrhea
- Rashes and other skin issues
- Mild blood count abnormalities
- Mild electrolyte abnormalities
Dangerous side effects (call right away)

• New or sudden shortness of breath, especially at rest, or associated with new or worse swelling in the legs
• Chest pains
• Yellowing of the skin/eyes (liver abnormalities)
• Severe headache
• Foamy urine
Special side effects for Sunitinib (Sutent), regorafenib (Stivarga), and pazopanib (Votrient)

- High blood pressure – almost everyone
- Bleeding and clots
- Yellowish or pale skin, hair and nails
- Watch that thyroid and liver!
- Hand-foot syndrome
# Management tricks

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid retention/swelling</td>
<td>Daily weights – salt intake – diuretics – massage – support stockings</td>
</tr>
<tr>
<td>Nausea/vomiting/abdominal pain</td>
<td>Anti-emetics – change time of day – take with food – small frequent meals - liver – small frequent meals – watch interacting meds -</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Rule out contributing causes - Prioritize activities – water – sleep/stress/exercise- meds</td>
</tr>
<tr>
<td>Aches and pains</td>
<td>Hydration – electrolytes – exercise – ivory soap – avoid OTC pain meds – Lidoderm patches/hot/cold</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Food diary – small frequent bland meals – yogurt – water - meds</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>Awareness – anti-emetics – high calories – grazing – supplements - meds</td>
</tr>
<tr>
<td>Labs to watch</td>
<td>CBC - Liver – Kidneys - Thyroid (especially long term)</td>
</tr>
</tbody>
</table>
What about generic imatinib?

- Patent expired for CML, not GIST, but generics are now available
- Generic companies required to prove bioequivalence, but not therapeutic equivalence
- Usual concerns with different side effects based on fillers as with any generic
- Brand-name only assistance programs

Good source of info - https://liferaftgroup.org/generics/
Take-home recommendations

- Know about GIST
  - Foundation websites, Days of Learning, forums

- Know about your own GIST
  - Customize treatment based on the mutations and distribution of tumors (Dr. Trent’s talk!)

- Know your options
  - Seek second opinions with GIST experts who are up-to-date on the newest drugs, clinical trials, science and research.
Thank you for coming today!

Questions???

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