Case Presentation

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March 18, 2005
Gastrointestinal Stromal Tumors: A Molecular and Surgical Approach
What is GIST?

- <1% all primary GI cancers.
- Most common form of mesenchymal (connective) tumors of the GIT.
- 15-20% small bowel malignancies.
- ~5000 cases per year in US.
- Occurs in 5\textsuperscript{th} – 7\textsuperscript{th} decade.
- Incidence probably underestimated previously.
Historical Evolution

1940’s- late 1960’s- Defined as smooth muscle neoplasm

1970’s- EM showed that only a few of these tumors has smooth muscle differentiation

1983- Mazur and Clark coined the neutral term ‘Gastric Stromal Tumor’ after revealing that many SMT lacked the immunohistochemical or EM evidence of smooth muscle.

Where do these tumor cells originate from?

- Originate from stem cells that differentiate towards the interstitial cells of Cajal (ICC).
- ICC arise from precursor mesenchymal cells that intercalate between nerve fibers and muscle cells in the adult intestine acting as pacemaker cells of the GIT, with regulation of peristalsis.
- Both ICC and GIST express KIT protein and have similar ultrastructural features.
- Not all GISTs arise from ICC, as some come from the mesentery or omentum which lack ICCs, suggesting an origin in multipotential mesenchymal stem cells.

ICC
C-KIT: A Defining Marker

- KIT, a 145-KD transmembrane glycoprotein, is the product of the c-kit (CD117) proto-oncogene.
- A member of the tyrosine kinase receptor.
- The kit receptor can be detected by IHC staining for CD117, a cell surface antigen on the extracellular domain of the KIT receptor.
- Stem-cell factor (SCF), also known as Steel factor (SLF), is the ligand for Kit.
- Binding of SLF to Kit results in receptor homodimerization, activation of KIT tyrosine kinase activity, and resultant phosphorylation of a variety of substrates that serve as effectors of intracellular signal transduction.
- This activation of signal transduction pathways leads to cellular growth and proliferation.
Figure 2. Schematic structure of the c-Kit tyrosine kinase. The extracellular domain of the c-Kit receptor binds to the ligand SCF. Tyrosine kinase activity resides in the intracellular domain of the protein, which is where Gleevec binds to c-Kit.
A. Ligand binding site
   - Membrane
   - Cytoplasm
   - JM
   - TK1
   - TK2

B. Membrane
   - Cytoplasm
   - SCF
   - SCF

C. Membrane
   - Cytoplasm
   - SCF
   - SCF
   - P

D. Membrane
   - Cytoplasm
   - SCF
   - SCF
   - P
   - P
   - P
Figure 3. c-Kit signal transduction. Binding of the ligand SCF to the c-Kit tyrosine kinase receptor causes the receptor to dimerise, auto-phosphorylate, and become activated. Recruitment of other signalling proteins into a signalling complex then initiates a signal transduction cascade with some final steps occurring in the nucleus.
Hirota et al investigated the mutational status of c-kit in mesenchymal tumors of the GI tract. They examined 49 mesenchymal tumors that were diagnosed as gastrointestinal stromal tumors.

- 94% (46/49) of these expressed KIT.
- 82% (40/49) CD34-positive
- 78% (38/49) positive for both KIT and CD34

Demonstrated that ICC were positive for kit and CD34.

They also demonstrated that mutations of c-kit resulted in gain of function of the enzymatic activity of the KIT tyrosine kinase.

These mutations result in:
- Auto-phosphorylation of c-kit
- Ligand-independent tyrosine kinase activity
- Stimulation of downstream signaling pathways leading to uncontrolled cell proliferation.
Clinical Presentation

- Occur in middle ages and older persons.
- Range in size from millimeters to 40 cm.
- Average tumor size at diagnosis 8cm.
- Often asymptomatic and discovered incidentally.
- Commonest presentation is palpable abdominal mass (50-70%), GI bleeding (30%), and abdominal pain (20%).
- Abdominal fullness, obstruction or perforation.
- 30% metastatic or locally infiltrating.
Relative frequencies of the occurrence of GISTs at different sites, and estimated frequencies of malignant tumors at different sites

<table>
<thead>
<tr>
<th>Site</th>
<th>Estimated percentage of all GISTs</th>
<th>Estimated frequency of malignant behavior</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophagus</td>
<td>1-3%</td>
<td>Great majority</td>
</tr>
<tr>
<td>Stomach</td>
<td>60-70%</td>
<td>25%</td>
</tr>
<tr>
<td>Small intestine</td>
<td>25-30%</td>
<td>50%</td>
</tr>
<tr>
<td>Duodenum</td>
<td>5%</td>
<td>30-40%</td>
</tr>
<tr>
<td>Colon</td>
<td>1%</td>
<td>Great majority</td>
</tr>
<tr>
<td>Rectum</td>
<td>5%</td>
<td>30-40%</td>
</tr>
<tr>
<td>Omentum and mesenteries</td>
<td>&lt;5%</td>
<td>50%</td>
</tr>
<tr>
<td>Widely metastatic in abdomen</td>
<td>5%</td>
<td>–</td>
</tr>
</tbody>
</table>
Diagnosis

- AXR
- Endoscopy
- CT scan
- Percutaneous Biopsy
Gastric GIST
Gastric GIST
Rectal GI ST
Histological Characterization

Spindle (70%)  Epitheloid (30%)
Low Risk versus High Risk
Immunohistochemistry

- Essential for the diagnosis.
- The distinction between GISTs and other tumors can be difficult by light microscopy alone.
# Immunohistochemistry

Immunohistochemical differential diagnosis of the most important mesenchymal tumors of the GI-tract. Key: + positive; +/- positive or negative; -/+ negative, a minority of cases positive; -/(+) negative, occasionally positive.

<table>
<thead>
<tr>
<th></th>
<th>KIT</th>
<th>CD34</th>
<th>Nestin</th>
<th>SMA</th>
<th>Desmin</th>
<th>S100</th>
<th>GFAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>GIST</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
<td>-/+</td>
<td>-/(+)</td>
<td>-/(+)</td>
<td>-</td>
</tr>
<tr>
<td>Leiomyoma</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>-/(+)</td>
<td>-/(+)</td>
<td>?</td>
<td>+</td>
<td>+/(−)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Schwannoma</td>
<td>-</td>
<td>-/(+)</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Undifferentiated sarcoma</td>
<td>-</td>
<td>-</td>
<td>?</td>
<td>-/(+)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

- 95% c-Kit (CD 117)
- 60-70% CD 34
- 20-30% SMA
- 5% S-100
- 1-2% Desmin
Predictors of Behavior

- Size
- Mitotic rate
- Location
- Incomplete Surgical Resection
- Tumor Rupture
Prognostic Factors


<table>
<thead>
<tr>
<th>Table 1. Prognostic Factors for Malignancy in GIST*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of Malignancy</td>
</tr>
<tr>
<td><strong>Low</strong></td>
</tr>
<tr>
<td>Tumour size: &lt;5 cm</td>
</tr>
<tr>
<td>Cellularity: Low</td>
</tr>
<tr>
<td>Necrosis: Absent to minimal</td>
</tr>
<tr>
<td>Mitoses: &lt;5 per 50 HPF</td>
</tr>
<tr>
<td>Growth pattern: No infiltration</td>
</tr>
<tr>
<td>c-kit mutation: Absent</td>
</tr>
<tr>
<td><strong>High</strong></td>
</tr>
<tr>
<td>Tumour size: &gt;5 cm</td>
</tr>
<tr>
<td>Cellularity: High</td>
</tr>
<tr>
<td>Necrosis: May be prominent</td>
</tr>
<tr>
<td>Mitoses: &gt;5 per 50 HPF</td>
</tr>
<tr>
<td>Growth pattern: May invade adjacent structures</td>
</tr>
<tr>
<td>c-kit mutation: Frequently present</td>
</tr>
</tbody>
</table>

HPF = high-powered field, 400X (high magnification microscopy).
Guidelines for the evaluation of malignancy of GISTs. Modified from Miettinen et al. [ref. 87]

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probably benign</td>
<td></td>
</tr>
<tr>
<td>Intestinal tumors</td>
<td>Maximum diameter less than 2cm and no more than 5 mitoses per 50 HPF</td>
</tr>
<tr>
<td>Gastric tumors</td>
<td>Maximum diameter less than 5cm and no more than 5 mitoses per 50 HPF</td>
</tr>
<tr>
<td>Malignant</td>
<td></td>
</tr>
<tr>
<td>Intestinal tumors</td>
<td>Maximum diameter over 5cm or more than 5 mitoses per 50 HPF</td>
</tr>
<tr>
<td>Gastric tumors</td>
<td>Maximum diameter over 10cm or more than 5 mitoses per 50 HPF</td>
</tr>
<tr>
<td>Uncertain or low malignant potential</td>
<td></td>
</tr>
<tr>
<td>Intestinal tumors</td>
<td>Maximum diameter 2 - 5cm and no more than 5 mitoses per 50 HPF</td>
</tr>
<tr>
<td>Gastric tumors</td>
<td>Maximum diameter 5 - 10cm or no more than 5 mitoses per 50 HPF</td>
</tr>
</tbody>
</table>
Disease Specific Survival After Complete Resection

Treatment Options

- Surgery
- Radiation/Chemotherapy
- Tyrosine Kinase Inhibitors
Surgery

- Only treatment option that can definitively cure the disease.
- Standard initial treatment for non-metastatic disease.
- Excise en-bloc, avoid tumor spillage.
- Lymphadenectomy not indicated.
- 5 year survival in multiple studies noted to be 48%-65% after complete resection.
Radiation/Chemotherapy

- Rarely used.
- Highly radio-resistant combined with the radio-sensitivity of adjacent organs.
- Chemotherapy response rates only 10-15% with multiple drug regimens.
<table>
<thead>
<tr>
<th>Regimen</th>
<th>n</th>
<th>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>DOX + DTIC+ IF</td>
<td>11</td>
<td>3 (27%)</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>NR (0–8%)</td>
</tr>
<tr>
<td>EPI + IF</td>
<td>13</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Various (e.g., DOX, gemcitabine, CT2584)</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>TOTAL</td>
<td>266</td>
<td>22 (8.3%)</td>
</tr>
</tbody>
</table>
Molecularly Targeted Therapy

- Since activation of Kit plays a crucial role in the pathogenesis of GIST, inhibition of Kit would be therapeutic.

- Imatinib (Gleevec) is a competitive and relatively selective antagonist of ATP binding that blocks the ability of c-Kit to transfer phosphate groups from ATP to tyrosine residues on substrate proteins, which in turn interrupts c-kit mediated signal transduction.
Gleevec
Duffaud et al. Oncology 2003
http://www.glivec.com/content/gist_video.html
Proof of Concept Study

- 50 year old female with metastatic GIST diagnosed in 1996.
- Liver metastases and multiple small intra-abdominal metastases were excised in 1998.
- Seven cycles of chemotherapy with doxorubicin, ifosfamide, and dacarbazine with no response.
- In March 1999 had bowel obstruction found at laparotomy to have diffuse intra-abdominal mets.
- Received thalidomide and α-interferon with no response.
- Treatment with 400 mg Imatinib once daily was started in March 2000.

Results

- MRI:
  - 2wks: 41% reduction tumor size
  - 8Mo: 75% reduction tumor size
  - 14Mo: >80% reduction tumor size
- Biological Response: Needle biopsy liver showed dramatic reduction in Kit positivity.
- FDG-PET scan: 4 weeks
Phase II Trial: Study Design

- Assess the clinical activity of Gleevec as reflected by objective response rates.
- Initiated July 2000
- Patients with unresectable or metastatic GIST were randomized to receive 400 or 600 mg of Gleevec per day.
- 147 patients enrolled.
- CR, PR, stable disease, progressive disease.
<table>
<thead>
<tr>
<th>Demographic variable</th>
<th>400mg (n=73)</th>
<th>600mg (n=74)</th>
<th>All Doses (N=147)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>56.6</td>
<td>52.2</td>
<td>54.4</td>
</tr>
<tr>
<td>Median</td>
<td>59</td>
<td>52</td>
<td>54</td>
</tr>
<tr>
<td>Range</td>
<td>28–83</td>
<td>18–79</td>
<td>18–83</td>
</tr>
<tr>
<td>Sex M:F (%)</td>
<td>60%:40%</td>
<td>53%:47%</td>
<td>56.5%:44.5%</td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>94.5%</td>
<td>90.5%</td>
<td>92.5%</td>
</tr>
<tr>
<td>Black</td>
<td>1.4%</td>
<td>5.4%</td>
<td>3.4%</td>
</tr>
<tr>
<td>Oriental</td>
<td>2.7%</td>
<td>2.7%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Other</td>
<td>1.4%</td>
<td>14%</td>
<td>1.4%</td>
</tr>
<tr>
<td>ECOG status (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 0</td>
<td>38.4%</td>
<td>45.9%</td>
<td>42.2%</td>
</tr>
<tr>
<td>Grade 1</td>
<td>38.4%</td>
<td>39.2%</td>
<td>38.8%</td>
</tr>
<tr>
<td>Grade 2</td>
<td>21.9%</td>
<td>14.9%</td>
<td>18.4%</td>
</tr>
<tr>
<td>Grade 3</td>
<td>1.4%</td>
<td>0</td>
<td>0.7%</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Site of initial tumour (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small Intestine</td>
<td></td>
<td></td>
<td>49%</td>
</tr>
<tr>
<td>Stomach</td>
<td></td>
<td></td>
<td>34%</td>
</tr>
<tr>
<td>Liver</td>
<td></td>
<td></td>
<td>17%</td>
</tr>
<tr>
<td>Peritoneum</td>
<td></td>
<td></td>
<td>12.9%</td>
</tr>
<tr>
<td>Omentum</td>
<td></td>
<td></td>
<td>11.6%</td>
</tr>
<tr>
<td>Site of recurrent tumour (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td></td>
<td></td>
<td>78%</td>
</tr>
<tr>
<td>Peritoneum</td>
<td></td>
<td></td>
<td>38%</td>
</tr>
<tr>
<td>Retroperitoneum</td>
<td></td>
<td></td>
<td>14%</td>
</tr>
<tr>
<td>Prior treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
<td>98%</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td></td>
<td></td>
<td>51%</td>
</tr>
<tr>
<td>Hormonal/Immunotherapy</td>
<td></td>
<td></td>
<td>1%</td>
</tr>
</tbody>
</table>
**Table 2.** Responses to Imatinib in Patients with Advanced Gastrointestinal Stromal Tumors.*

<table>
<thead>
<tr>
<th>Best Response</th>
<th>400 mg (N=73)</th>
<th>600 mg (N=74)</th>
<th>Either Dose (N=147)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>36 (49.3 [37.4–61.3])</td>
<td>43 (58.1 [46.1–69.5])</td>
<td>79 (53.7 [45.3–62.0])</td>
</tr>
<tr>
<td>Stable disease</td>
<td>23 (31.5 [21.1–43.4])</td>
<td>18 (24.3 [15.1–35.7])</td>
<td>41 (27.9 [20.8–35.9])</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>12 (16.4)</td>
<td>8 (10.8)</td>
<td>20 (13.6)</td>
</tr>
<tr>
<td>Could not be evaluated</td>
<td>2 (2.7)</td>
<td>5 (6.8)</td>
<td>7 (4.8)</td>
</tr>
</tbody>
</table>

*CI denotes confidence interval.

Phase II: Con’d

- 86% of tumor specimens analyzed (72 patients) had activating mutations of KIT
  - 71% exon 11
  - 14% exon 9
  - 1% exon 17

- Patients whose tumor had no detectable KIT mutation were eight times more likely to have primary progression in response to Gleevec (44%) compared with patients whose tumor expressed an exon 11 activating KIT mutation.

- Early registration approval from FDA in February 2002.
Unanswered Questions?

- What is the right dose?
- Duration of therapy?
- Will neoadjuvant therapy improve outcome?
- Will adjuvant therapy improve outcome?
- Influence of mutations on response to therapy?
- Role of surgery in recurrence?
Southwest Oncology Group (S0033)- Dosage

  - 746 patients
  - Response rates 43% for both
  - Two year progression free 50% LD vs. 53% HD
  - Two year survival estimates 78% LD vs. 73% HD
  - Higher dose not significantly better.

  - 946 patients
  - RR: 50% LD vs. 54% HD
  - Two year survival: 69% LD vs. 74% HD
  - Two year progression free survival: 44% LD vs. 50% HD
# Management of Selected Imatinib-Related Toxicities: NCCN* Recommendations

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Management strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute decrease in hemoglobin of &gt;2 g/dL</td>
<td>Withhold imatinib until hemoglobin stabilized; transfusion or surgical intervention if bleeding does not resolve</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>Antacids or proton pump inhibitors</td>
</tr>
<tr>
<td>Dyspepsia/gastrointestinal side effects</td>
<td>Mitigate by having patient take the drug with food</td>
</tr>
<tr>
<td>Fluid retention (common)</td>
<td>Patients with &gt;5-lb increase in weight during 1 week should be counseled to decrease dietary salt; consider addition of furosemide, with judicious dosing to avoid intravascular volume depletion†</td>
</tr>
<tr>
<td>Leukopenia (rare)</td>
<td>Continue imatinib unless absolute neutrophil count (ANC) &lt;1,000/mm³</td>
</tr>
<tr>
<td>Liver function test abnormalities (&lt;5 percent of patients)</td>
<td>Withhold imatinib</td>
</tr>
<tr>
<td>Loose stools/ diarrhea</td>
<td>Loperamide hydrochloride; atropine sulfate/diphenoxylate hydrochloride</td>
</tr>
<tr>
<td>Muscle cramping</td>
<td>Mitigate by having patient increase regular oral fluid intake and possibly take quinine sulfate</td>
</tr>
<tr>
<td>Rash</td>
<td>Usually resolves with time; symptomatic management with topical or oral diphenhydramine helpful</td>
</tr>
</tbody>
</table>

* NCCN; National Comprehensive Cancer Network
† It is generally not necessary to decrease the dose of imatinib to manage edema, so long as it can be controlled with other supportive measures.
• Withholding imatinib should lead to recovery within several days; reinitiation without dose reduction is recommended and is often accomplished without recurrence of leukopenia. If patient continues to exhibit significant leukopenia, imatinib dose should be decreased.

Duration of Therapy

- French Trial in progress that is randomly assigning patients with advanced GIST and no evidence of progressive disease after one year of Gleevec to continuous therapy, or interruption of therapy until disease progression.

- Until results return continuous therapy advised until disease progression.

Adjuvant: Phase II ACSOG Z9000

- **High Risk**
  - Tumor >10cm
  - Tumor Rupture
  - Tumor Hemorrhage
  - Multifocal Tumors

- Must start within 84 days of resection.

- Continue for 1 year in the absence of recurrence or unacceptable toxicity.
Adjuvant: Phase III ACSOG (Z9001)

- Primary GIST ≥3 cm
  - Complete gross resection
    - Tumor Kit +
      - Placebo x 1 year
      - STI571 400 mg/day x 1 year
        - Survival Recurrence
Neoadjuvant Therapy

- Currently in the formulative stages.
- Radiographic Evidence
  - 4% CR
  - 35% PR
  - 37% Stable
  - 18% Progression
  - 2% Died
Median time to recurrence is 1.5 to 2 years.

Only 10% who undergo complete surgical resection are disease free after an average follow-up of 68 months (MD Anderson data).

5-Year Survival is about 50-65% after complete resection of localized GIST versus 35% with advanced disease.

A total of 40%-90% surgically resected patients have post-op recurrence or metastasis.

Most recur in the peritoneum and liver.
Influence on Mutations on Recurrence

- Approximately 90% of all GISTs have a c-Kit mutation.
- All Kit mutant isoforms were associated with a clinical response:
  - Exon 11: 84% PR
  - Exon 9: 48% PR
- Time to treatment failure
  - Exon 11: 687 days
  - Exon 9: 200 days

Peritoneal Metastasis

- Cytoreductive surgery followed by intraperitoneal chemotherapy with cisplatin and doxorubicin or mitoxantrone for peritoneal recurrence.

- In 27 patients with disease isolated to the peritoneum, the median time to recurrence was increased from 8 months with surgery alone to 21 months with the addition of intraperitoneal mitoxantrone.

- Presently, only indicated for patients whose tumors are resistant to Gleevec.

Liver Metastasis

131 patients at MSKCC with liver mets
- 34 (26%) underwent complete resection of all gross disease.
- No peri-operative deaths
- 1 and 3-yr survival were 90% and 58%.
- Survival was predicted by the time interval between the resection of the primary tumor and the development of liver mets.
Liver Mets


**Treatment Algorithm**

- **GIST (CD117+)**
  - **Resectable**
    - Complete resection
    - Low-risk
      - Size < 5 cm
      - Negative margin
      - Mitoses < 1/10 hpf
      - Necrosis absent
    - Careful observation
  - Gross residual disease
    - High-risk
      - Size > 5 cm
      - Positive margin
      - Mitoses > 1/10 hpf
      - Necrosis present
      - Tumor rupture
      - Tumor hemorrhage
    - Clinical trial of adjuvant imatinib
  - Imatinib mesylate (STI-571, Gleevec®)
    - Tumor progression
    - Imatinib dose escalation or Clinical trial of investigational agent or Palliation
    - Re-evaluate resectability
  - Clinical response
    - Re-evaluate resectability
    - Enrollment in the ACSOG Z9001 trial of adjuvant imatinib includes tumors > 3 cm.
Summary

- GIST tumors are more common than previously observed.
- IHC is essential for the diagnosis.
- The application of Imatinib represents a major paradigm shift in cancer therapy, targeting the specific molecular abnormalities crucial in the etiology of cancer.
- Clinical trials are in the process of elucidating the role of Imatinib for adjuvant and neo-adjuvant purposes.
Questions

What are the FDA approved indications for Imatinib?

A. Completely resected GIST with negative margins
B. Metastatic GIST
C. Locally unresectable GIST
D. Incompletely excised GIST
E. B and C

Which IHC marker is most specific for GIST?

A. CD-34
B. CD-117
C. c-KIT
D. S-100
E. B and C
Questions

Which test is most sensitive for early monitoring of Gleveec efficacy?
- A. CT Scan
- B. AXR
- C. Ultrasound
- D. PET Scan

What is the most common location of GIST?
- A. Rectum
- B. Small Bowel
- C. Stomach
- D. Esophagus
- E. None of the above