The emerging role of imatinib blood level testing in advanced GIST

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Disclosures

- Pfizer, Novartis – Advisory Board
We have learned a tremendous amount regarding GIST in the past decade:

- Importance of KIT signaling
- Application of tyrosine kinase inhibition
- Diverse mechanisms of TKI resistance
- Ongoing efforts to develop novel therapeutic strategies, both medical and surgical, to combat resistance
A retrospective Swedish study determined that 72% of GI tumors now identified as GIST had been originally classified as other tumors.

Finding the Critical Kinase Mutation in the Gastrointestinal Sarcoma: GIST

Gain-of-Function Mutations of c-kit in Human Gastrointestinal Stromal Tumors

Seiichi Hirota,* Koji Isozaki,* Yasuhiro Moriyama, Koji Hashimoto, Toshiro Nishida, Shingo Ishiguro, Kiyoshi Kawano, Masato Hanada, Akihiko Kurata, Masashi Takeda, Ghulam Muhammad Tunio, Yuji Matsuzawa, Yuzuru Kanakura, Yasuhisa Shinomura, Yukihiro Kitamura†

Mutations Generate Uncontrolled Constant Activation of Receptor Tyrosine Kinases in GIST

RTK mutations in GIST allow for constitutive activation in the absence of ligand binding.
Tyrosine Kinase inhibition in GIST: Imatinib Mesylate

- Imatinib mesylate occupies ATP binding pocket of KIT kinase domain
  - Prevents substrate protein phosphorylation and signaling
  - Lack of signaling inhibits proliferation and survival

Inhibiting TKI signaling with imatinib leads to dramatic disease control in GIST

Blanke et al, JCO 2008
Median followup 71 months – B2222
With a dramatic improvement in Overall Survival
Location of activating *KIT* and *PDGFRA* mutations in GISTs vary.

**KIT**
- Exon 9 (8.3%)
- Exon 11 (75.9%)
- Exon 13 (1.2%)
- Exon 17 (0.9%)

**PDGFRA**
- Exon 12 (0.3%)
- Exon 13 (1.2%)
- Exon 17 (0.9%)
- Exon 18 (0.6%)

Overall Mutation Frequency: **87.3%**
GIST

- Heterogeneous Disease

- Prognostic Factors
  - Primary Disease – risk of recurrence
    - Primary site of disease – gastric vs small bowel
    - Tumor size at presentation – small vs large
    - Number of mitoses/ 50Hpf – low vs high
## GIST Tumor Characteristics and Risk of Progression

<table>
<thead>
<tr>
<th>Group</th>
<th>Size, cm</th>
<th>Mitotic rate per 50 HPFs</th>
<th>Gastric GISTs</th>
<th>Small Intestinal GISTs</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>% of Pts</td>
<td>Malig Pot</td>
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<td>1</td>
<td>≤ 2</td>
<td>≤ 5</td>
<td>0</td>
<td>Very low if any</td>
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<tr>
<td>2</td>
<td>&gt; 2, ≤ 5</td>
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<td>1.9</td>
<td>Low</td>
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<tr>
<td>3a</td>
<td>&gt; 5, ≤ 10</td>
<td>≤ 5</td>
<td>3.6</td>
<td>Low</td>
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<tr>
<td><strong>3b</strong></td>
<td>&gt; 10</td>
<td>≤ 5</td>
<td>12</td>
<td>Intermediate</td>
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<tr>
<td>4</td>
<td>≤ 2</td>
<td>&gt; 5</td>
<td>0</td>
<td>Low*</td>
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<tr>
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<td>&gt; 2, ≤ 5</td>
<td>&gt; 5</td>
<td>16</td>
<td>Intermediate</td>
</tr>
<tr>
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<td>&gt; 5</td>
<td>55</td>
<td>High</td>
</tr>
<tr>
<td>6b</td>
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<td>&gt; 5</td>
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*Denotes tumor categories with very small numbers of cases insufficient for prediction of malignant potential.

HFPs = High-power fields

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GIST

- Heterogeneous Disease

- Predictive Factors
  - Response to Therapy
    - Presence of activating mutation – KIT, PDGFR
    - Location of activating mutation – KIT exon 11, exon 9, others
Patients with metastatic GIST have different clinical outcomes based on tumor mutational status when treated with imatinib
In the lab, there are different sensitivities to TKIs based on the location of the KIT mutation in GIST.

Exon 11

IM IC50: 15nM
SU IC50: 8nM

Stephen Swank, Lab of Jonathan Fletcher, MD DFCI/BWH
In the lab, there are different sensitivities to TKIs based on the location of the KIT mutation in GIST

Stephen Swank, Lab of Jonathan Fletcher, MD DFCI/BWH
Can dose overcome some of this difference in sensitivity?

- In the lab, perhaps higher exposure of IM is needed to control cells which harbor exon 9 mutations compared to those which harbor exon 11 mutations.

- Does this correlate clinically?
Higher dose imatinib may provide benefit to specific molecular subtypes of GIST – exon 9

But not to others……

Patients with Tumors with KIT Exon 11 Mutations

Number of patients at risk:

<table>
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<tr>
<th>Treatment</th>
<th>400 mg</th>
<th>800 mg</th>
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</thead>
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<tr>
<td>400 mg</td>
<td>118</td>
<td>130</td>
</tr>
<tr>
<td>800 mg</td>
<td>94</td>
<td>113</td>
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<tr>
<td></td>
<td>53</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>22</td>
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What does this have to do with imatinib blood levels?

- There are many variables which may affect outcome
  - Patient characteristics: pediatric, adult
  - Tumor characteristics: size, extent of disease, mutational status
  - Treatment characteristics: dose of IM

- In this wide array of factors how much does IM blood level play a role in the outcome of patients with GIST? Is the impact independent of dose?
Imatinib Blood Levels

- Imatinib high oral bioavailability in humans
- Imatinib pK extensively studied in early Phase I/II in imatinib in both CML and GIST
- Excellent correlation between IM Cmin (trough level), Cmax (peak level) and AUC (exposure)
What is the correlation of IM blood level to outcome in CML?
Mean IM Trough Levels were higher for patients who achieved Major Molecular Response in CML- independent of dose (400mg vs 600mg)

N=68

Comparison of mean IM C min  p=0.03

Mean IM trough levels were higher for patients who responded to imatinib therapy – all patients treated at the same dose (400mg/day)

Comparison of mean IM C min  p=0.01

What do we know about IM Blood Levels in GIST
Significant inter-patient variability of IM levels in GIST patient at 400mg/d
D29 IM trough Levels were obtained in the Randomized Phase II trial in GIST – B2222

- Metastatic GIST
  - Imatinib 400mg daily
  - Imatinib 600mg daily

Imatinib trough levels (Cmin) drawn at steady state (d29)

Patients followed for Response (WHO), PFS, OS
Wide Distribution of IM exposure without clear correlation with dose

Demetri et al. JCO 2009
Median Imatinib trough level did not correlate with Clinical Benefit in GIST

57 pts (78%) achieved PR, CR or SD

<table>
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<th>Median Cmin ng/mL</th>
<th>Range</th>
<th>25% - 75%</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=57 PR,CR or SD</td>
<td>1446</td>
<td>414-3336</td>
<td>1204 -2062</td>
</tr>
<tr>
<td>N=16 PD or na</td>
<td>1155</td>
<td>545-4182</td>
<td>1041 - 1562</td>
</tr>
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Demetri et al. JCO 2009
GIST Patients whose IM exposure was in the lowest Quartile had a shorter PFS

Fig 3. Time to progression by imatinib day 29 trough level ($C_{\text{min}}$) quartile (Q).

Demetri et al. JCO 2009
Additional information...

- No apparent increase in reported grade 3/4 toxicity for patients in higher Quartiles

- Not enough data on molecular subtypes to draw definitive conclusions about relationship between genotype, drug level and response
Higher exposure to imatinib may correlate with a greater number of side effects

Conclusions

- Retrospective data suggests there may be a relationship between IM trough levels and progression free survival in patients with metastatic GIST.

- IM trough level appears to be independent of dose (400mg vs 600mg) – however, not clear if also independent of dose for IM 800mg/d.

- Other clinical and biologic variables also contribute to clinical outcome – the relative impact of IM trough levels is not yet known.
Conclusions (con’t.)

- “Optimal level” of drug exposure has yet to be prospectively confirmed for GIST

- Based on our understanding of GIST, there may be different “optimal levels” depending on the characteristics of the patient and the tumor

- Are drug blood levels relevant to outcomes for other TKIs??
Because of these ongoing questions prospective trials are needed to determine the optimal role of TKI blood level testing, if any, to improve the outcome of patients with GIST.
First line met GIST
Imatinib 400mg/day
For a minimum of 4 wks

Continue 400mg/d

>1000 ng/mL
IM Cmin

<1000 ng/mL
Randomize

Continue 400mg/d

Dose escalation to
Goal IM BLT
of >1000 ng/mL
Max dose 800mg/d
Thank you