Modern Management of Metastatic GIST: Success, Challenges and Future Directions

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GIST Day of Learning
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Disclosures

• Research Support
  – Pfizer, Bayer, Novartis, Blueprint Medicines, Deciphera

• Consulting
  – Bayer, Novartis, Blueprint Medicines, Deciphera, Astra Zeneca, Eli Lilly, Exilexus
Learning Objectives

• Review the current standard of care systemic therapies for metastatic GIST in the first, second and third line settings

• Discuss the primary mechanisms of TKI resistance in GIST

• Review management of resectable, localized GIST
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, Toshirou Nishida, Shingo Ishiguro, Kiyoshi Kawano, Masato Hanada, Akihiko Kurata, Masashi Takeda, Ghulam Muhammad Tunio, Yuji Matsuzawa, Yuzuru Kanakura, Yasuhisa Shinomura, Yukihiro Kitamura†

Science 279:577-580, 1998
RTK mutations in GIST allow for constitutive activation in the absence of ligand binding.
The Constitutively Active Kinase in GIST cells can be Shut OFF by a Drug (Imatinib)

Hours After Imatinib

0  1  9  24  48

Anti-PhosphoTyrosine

Total KIT

KIT Protein is still present

S0033 Study Design: Randomized Phase III trial of imatinib at 400 vs. 800 mg/d for advanced KIT-expressing GIST

- Multicenter, randomized, phase III Intergroup study
- FULLY ACCRUED between December 2000 – September 2001
- 746 patients entered, 695 fully eligible

Metastatic/unresectable GIST pts (n=746 entered) → Randomization

Imatinib 400 mg/day → Disease progression

Imatinib 800 mg/day → Optional cross-over (n=130) → Disease progression

OFF STUDY TREATMENT
Median PFS
19 months

NO DIFFERENCE IN LONG-TERM SURVIVORS BETWEEN STUDY ARMS: 27% in 400/day vs. 25% in 800/day

Demetri et al, ASCO 2014
**KIT and PDGFRA Mutations in 324 KIT-expressing GISTs**

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

- **PDGFRA**
  - Exon 12 (0.3%)
  - Exon 18 (0.6%)

**Overall Mutation Frequency:** 87.3%
S0033 Overall Survival by GIST Genotype – 2014 data

Significantly worse OS for *KIT* exon 9 mutant vs. *KIT* exon 11 mutant

- *KIT* exon 9 mutant: $P = 0.001$
- No Mutation (WT): $P = 0.047$

Median OS (months):
- *KIT* exon 11: 66
- No Mutation (WT): 40
- *KIT* exon 9: 38

Demetri et al, ASCO 2014
Despite these dramatic results – resistance to imatinib remains a major challenge in the advance disease setting
Post-imatinib resistance is characterized by secondary KIT mutations which occur in a non-random pattern - highlights the continued importance of KIT in the resistant setting

Modified from Heinrich et al. JCO 2006, JCO 2008

ATP Binding pocket

Activation Loop

1. V654A, D816H (patient 5 this report)
2. D820E, N822K, N822Y (patient 39 this report)
3. V654A, N822K (Antonescu et al17)
4. D816E, D820V, D820E, N822K (Wardemann et al12)
5. V654A, T670E, Y823D (Wardemann et al12)
7. V654A, T670I (Wardemann et al15)
Sunitinib – approved second line therapy in GIST
Sunitinib binds in the intracellular ATP-binding pocket of KIT

Courtesy of K Gajiwala and G Demetri

Gajiwala et al. Proc Natl Acad Sci USA 2009;106:1542
Time to Tumor Progression significantly longer with sunitinib vs placebo in Phase III trial of imatinib resistant/refractory GIST

Sunitinib (n=207)
Placebo (n=105)

Median
27.3 weeks (Sunitinib)
6.4 weeks (control)

Hazard ratio = 0.33
95% CI (0.23, 0.47)
p < 0.00001

Demetri et al, Lancet 2006
Although sunitinib has broader inhibitory profile beyond KIT, it is likely that the primary benefit in GIST is related to broader spectrum of KIT inhibition.
Activity in the second line – due to broader KIT inhibition – but also differences in toxicity due to broader profile of inhibition

- Hand-Foot Skin Reaction
- Hypertension
- Oral hypersensitivity
Similarly, regorafenib – broad spectrum TKI with potent KIT inhibition

Kaplan-Meier survival analysis after treatment with regorafenib or placebo (A) Progression-free survival, per central review (primary endpoint, final analysis). (B) Overall survival (interim analysis). HR=hazard ratio. Demetri et al, Lancet, 2013
Regorafenib in GIST following failure of IM and SU:
Treatment related AEs of any grade occurring in >25% of pts

- Alopecia
- Anemia
- Anorexia
- Diarrhea
- Fatigue
- Hand-Foot Skin reaction
- Headache
- Hoarseness
- Hypertension
- Hypophosphatemia
- Lipase elevation
- Oral Mucositis
- Myalgia
- Nausea

Phase II trial of Regorafenib in GIST. George, et al, JCO 2012
TKI sensitivity varies based on location of mutation

**KIT Secondary Kinase Mutations**

- V654A, D816H (patient 5 this report)
- D820E, N822K, N822Y (patient 39 this report)
- V654A, N822K (Antonescu et al.)
- D816E, D820V, D820E, N822K (Wardelmann et al.)
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- V654A, D820G (Wardelmann et al.)
- V654A, T670I (Wardelmann et al.)

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**Imatinib**
- Sensitive
  - V654A
  - D816H
- Intermediate
  - D820E
- Resistant
  - N822K

**Sunitinib**
- Sensitive
  - V654A
  - D820G
- Intermediate
  - T670E
- Resistant
  - Y823D

**ATP Binding Pocket**

- Courtesy of J. Fletcher
TKI sensitivity varies based on location of mutation

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Imatinib

Sunitinib

Activation Loop
TKI sensitivity varies based on location of mutation

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Modified from Heinrich et al. JCO 2006, JCO 2008
TKI sensitivity varies based on location of mutation

Modified from Heinrich et al. JCO 2006, JCO 2008

ATP Binding Pocket

Imatinib
Sunitinib
Regorafenib

Courtesy of J. Fletcher
Progression of KIT Exon 13 imatinib-resistant subclone on regorafenib

KIT exon 13 (V654A). Radiographic and metabolic progression on regorafenib

Baseline

C12D21
Resection biopsy

exon 11 + exon 13 (V654A)
Response of *KIT* Exon 17 imatinib-resistant subclone on regorafenib

*KIT* exon 17 (D820Y). Radiographic and metabolic response on regorafenib

**Baseline**

Pre-regorafenib

**exon 11 + exon 17 (D820Y)**

**C4D21**

Serano et al, CTOS 2013 abstract 037
However, there is notable heterogeneity in resistance within individual patients and likely within individual tumors.
Progression on Imatinib: KIT exon 11 primary mut

DHPLC
prim. mut
ex.11
ex.11
ex.11
ex.11

Liegl et al. J Pathol. 2008 Sep;216(1):64-74

Courtesy of J. Fletcher
GIST Progression on IMATINIB: Mutational heterogeneity

DHPLC

prim. mut sec. mut.

Drug/ATP binding pocket

Sunitinib sensitive

Kinase activation loop

Sunitinib resistant

V654A

D820G

N822Y

N822Y

ex. 1

ex. 1

ex. 1

ex. 1

Liegl et al. J Pathol. 2008 Sep;216(1):64-74

Courtesy of J. Fletcher
Because tumor biopsies may be impractical to gain a sense of the landscape of heterogeneity, there is increasing interest in less-invasive approaches.
Ph2 Trial of Ponatinib in GIST
FDG-PET, Biopsy, Plasma Molecular Analysis Analysis

<table>
<thead>
<tr>
<th>Mutations</th>
<th>% reads</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td></td>
</tr>
<tr>
<td>ΔEx11</td>
<td>89</td>
</tr>
<tr>
<td>Secondary</td>
<td></td>
</tr>
<tr>
<td>Y823D</td>
<td>87</td>
</tr>
</tbody>
</table>

Heinrich et al, ASCO 2014
Significant heterogeneity of secondary mutations seen in a subset of patients

Number of Secondary Mutants Detected per Patient  
(n=37)\textsuperscript{a}

However full profile likely limited by mutations included in the BEAMing panel

\*Number of unique secondary mutants per patient observed across all samples analyzed.  
\**includes exon 9 (n=6), exon 13 (n=1), and exon 17 (n=1)

Heinrich et al, ASCO 2015, abstract 150094
Additional preliminary data suggests resistance mutations seen in cf DNA of GIST patients – emergence of KIT exon 17, continued heterogeneity

Bauer et al, ASCO 2015, abstract 10518
• Much of this discussion has focused on KIT mutant GIST, there are other, uncommon mutational subtypes of GIST which may require special consideration in the advanced disease setting
Management of Localized GIST
Management of localized GIST

NCCN Guidelines Version 2.2019
Gastrointestinal Stromal Tumors (GIST)

MASS SUSPICIOUS FOR GIST

RESULTS OF INITIAL DIAGNOSTIC EVALUATION

- Prior to the initiation of therapy, all patients should be evaluated and managed by a multidisciplinary team with expertise and experience in sarcoma
- For very small gastric GISTs < 2 cm (See GIST-2)
- Imaging
- Consider chest imaging
- Testing for mutations in KIT and PDGFRA is strongly recommended
- Genotyping should be performed when medical therapy is planned

Resectable with minimal morbidity

Pathology result and risk assessment

Resect mass

Consider preoperative imatinib to decrease surgical morbidity

Unresectable or metastatic disease

See Postoperative Treatment (GIST-6)

See (GIST-4)

See (GIST-3)
Pathologic and Molecular Features Correlate with Long Term Outcome of resected localized GIST – ACOSOG Z9001 update
Benefit of adjuvant imatinib appears most notable in patients with tumors >10cm – ACOSOG Z9001

Dematteo et al. Lancet 2009
ACOSOG Z9001 trial – imatinib vs placebo for 1 year following resection of localized GIST: Natural history of resected GIST: PLACEBO ARM

MITOTIC RATE is the strongest predictor of recurrence

Corless C L et al. JCO 2014;32:1563-1570
ACOSOG Z9001 trial – imatinib vs placebo for 1 year following resection of localized GIST: Natural history of resected GIST: PLACEBO ARM

No significant difference in recurrence by genotype

Corless C L et al. JCO 2014;32:1563-1570
ACOSOG Z9001 trial – imatinib vs placebo for 1 year following resection of localized GIST: Natural history of resected GIST: PLACEBO ARM

Unless one looks at subsets of exon 11: Del 557 558 have high Risk of recurrence

Corless C L et al. JCO 2014;32:1563-1570
Impact of Genotype on outcome in imatinib arm – Z9001

- Exon 11 RFS improved with imatinib
- Exon 9 not well balanced to draw conclusion
- “WT” GIST – no clear benefit
- Small number of PDGFR cases – appears to have benefit EXCEPT D842V
Improved recurrence free survival and overall survival in HIGH RISK patients treated with imatinib for 36 vs 12 months

Joensuu, H. et al. JAMA 2012;307:1265-1272

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The recommendations for adjuvant imatinib therapy by integration of the risk assessment (based on modified NIH classification) and tumor genotype [KIT ex. 9 p.A502_Y503dup, KIT ex. 11 (KITdel-inc557/558 and other), and PDGFRA ex. 18 (p.D842V and other)]


* Metastatic/locally advanced GIST with KIT ex. 9 mutations respond better to 800 mg imatinib daily (compared with the standard 400 mg). Therefore, increased dose may be considered in the adjuvant setting.
Conclusions

• We have learned a tremendous amount about GIST since 2000
• There is a subset of patients with advanced GIST who will remain with excellent disease control on imatinib for >10 years
• Second and third line therapies are effective, but non-KIT targets can lead to toxicity
• Heterogeneity of resistance mutations remains a challenge, increasing research ct DNA
• Strategies in development are focusing on more efficient KIT targeting
• Unique subsets of GIST, such as SDH def GIST and PDGFRa842V, will likely require unique approaches
THANK YOU!