Pediatric and Wildtype Updates

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NIH Pediatric and Wildtype GIST Patients

Pediatric 36%  Adults  64%
16 year old female

- Becomes very tired at the end of her varsity soccer games
- Sleeps in late
- Complains of vague stomach pains of three years duration
  often this is associated with lots of homework
Typical Pediatric GIST Patient

16 year old female

- Becomes very tired at the end of her varsity soccer games
- Sleeps in late
- Complains of vague stomach pains of three years duration often this is associated with lots of homework

- Then passes out or has black-colored stools
- CT shows a large bleeding mass in the bottom of the stomach and a smaller mass a few inches above that, there is a small nodule in the liver that is too small to be characterized
Typical Pediatric GIST Patient

Undergoes surgical resection to obtain tissue for diagnosis and to prevent further bleeding
Things You Need to Do

Get confirmation of the diagnosis
- Dana-Farber, MD Anderson, MSKCC, NIH, Oregon HSU

Organize a treatment team
- primary team at home, center that sees more GIST patients
- all of the above, Fox Chase, Miami, St Jude, Huntsman Utah

Plan for the future
- junior/senior prom, homecoming, college applications/interviews
- goal of the treatment team is to allow you to do everything that you want to do
Survival

5 year Overall Survival / Event Free Survival

Percent survival

Months

Overall Survival
Event Free Survival
<table>
<thead>
<tr>
<th>Characteristic</th>
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<th>adult wildtype (n = 45)</th>
<th>pediatric (n = 24)</th>
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## Clinical Characteristics

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<td>SDHB-negative</td>
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Succinate Dehydrogenase is

part of the Kreb’s cycle
part of the electron transport chain

A, B    catalytic units
C, D    membrane anchor proteins

AF1, AF2    assembly complex
GIST 4000

- KIT/PDGFRA (90%)
  - SDHB (+) (30%)
    - BRAF V600E (5%)
    - BRAF WT (25%)
    - Germline SDH (15%)
- Wildtype (10%)
  - SDHB (-) (70%)
    - No Mutation (55%)

30% of adults and no pediatrics
Most adults and almost all pediatrics
### SDHB-positive versus SDHB-negative

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<td>Age at diagnosis</td>
<td>39.7</td>
<td>24.2</td>
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<td>Stomach primary</td>
<td>25%</td>
<td>100%</td>
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<td>Overall survival</td>
<td>75%</td>
<td>96%</td>
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<td>Response to TKI</td>
<td>50%</td>
<td>3%</td>
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Hypothesis For SDHB(+) BRAF(wt) Patients

30 yo female or male with a single GIST lesion in the small intestine

These tumors are driven by:

. activating mutations in other exons of KIT/PDGFRA
. activating mutations in a gene very closely related to KIT and PDGFRA (either known or unknown)
. a non-TK, non-SDH dependent pathway

Clinical implications
neo-adjuvant TKI therapy with Imatinib/Sunitinib
surgery if response, then indefinite oral therapy
SDHB(-) Patients

This is a homogenous group of patients who have very similar clinical histories

Age at diagnosis 24.4 years (median 21, range 7-58)

15% harbor germline SDH mutations (B, C, D)

25% harbor a germline SDH mutation in (A)

30% do not have detectable mutations
Hypothesis For SDHB(-) Patients

These tumors are driven by loss of SDH activity and accumulation of succinate

Patients will have a germline mutation in SDH and a somatic loss of the remaining allele

or

Patients will have two somatic alterations in both alleles of a SDH gene
Patients with SDHB germline mutations show chromosomal loss at the SDHB locus

Joshua Schiffman  (Huntsman Cancer Center, University of Utah)
Other Family Members with SDH mutations

Radiographic and biochemical monitoring protocols
The Role of IGF-1R in WT GIST

89% (71/80)
SDHB(-) are IGF1R(+)

1% (9/625)
SDHB(+) are IGF1R(+)

the NIH pediatric GIST team

Art Therapist Megan Robb
Clinical Nurses Joan Sheeren, Patty McGinley
Complementary Medicine Coordinator Scott Miller
Dermatologist Sherri DePollar
Geneticists Heidi Kong
Constantine Stratakis, Margarita Raygada, Maya Lodish
Medical Oncologists Shivani Kumar
Nutritionist Jennifer Graf
Pediatric Oncologists Lee Helman, Su Young Kim
Radiologist Baris Turkbey, Peter Choyke
Research Nurses Christine Graham, Donna Bernstein, Lauren Long, Robyn Bent
Pain Specialist Ann Berger, Dan Handel
Pathologist Maria Tsokos
Psychosocial Specialist Lori Wiener
Rehabilitation Medicine Donna Gregory
Social Worker Barbara Santangini
Videography Demetrio Domingo
Thanks

To the physicians who volunteer
To the NIH GIST healthcare team
To LRG and GIST Support International
To the patients and their families

Becky Bensenhaver
Phyllis Gay
Julie Royster
those from GSI here today