Clinical Results from the NIH GIST Clinic and Identification of SDH Mutations

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the NIH Pediatric & Wildtype GIST Clinic

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Introduction

Gastrointestinal Stromal Tumor (GIST) is a rare disorder and pediatric patients appear to have a different clinical course from adults. Most adult GIST patients have activating mutations in the receptor tyrosine kinase KIT or PDGFRA and they respond to therapy using small molecule inhibitors of these kinases. Pediatric GIST patients do not have mutations (wildtype) in these genes and they do not respond as well as adults to therapy with these inhibitors. Chemotherapy and radiation therapy are ineffective and surgical resection is associated with a high recurrence rate. Despite these factors, children appear to have a more indolent pace of progression. Ten percent of adults have wildtype GIST, but it is unclear whether their clinical course is more similar to children, or to adults with KIT/PDGFRA mutated GIST. Therefore, we need to determine the natural history and biology of pediatric and wildtype GIST, in our efforts to identify new treatment regimens.

The NIH Pediatric and wildtype GIST Clinic is a bi-annual collaborative effort between clinicians, researchers, support groups and patients. **CPGR** is the **C**onsortium for **P**ediatric and wildtype **G**IST **R**esearch. There are 50 current CPGR participants from eight medical institutions and two GIST support groups. CPGR participants attend the Pediatric and wildtype GIST clinics hosted by the NIH and perform a host of laboratory and clinical research endeavors to define the changes that underlie wildtype GIST, in efforts to translate these findings into national trials. We encourage all those with similar interests to participate in CPGR.

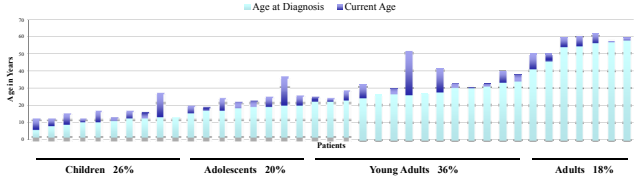
We have also opened a website dedicated to Pediatric and wildtype GIST
www.pediatricgist.cancer.gov

Patients who wish to register for subsequent clinics at the NIH should contact
ncipediatricgist@nih.mail.gov

CPGR Consortium for Pediatric and GIST Research

Patients who are able to submit tissue samples for clinical and research purposes should contact, Dr. Su Young Kim, for further information, kimsuyou@mail.nih.gov

Patient Characteristics



Each bar on the graph represents a patient (x-axis) and the height of the bar (y-axis) depicts the age at diagnosis and the current age of 39 patients who have attended the Pediatric and wildtype GIST clinic at the NIH.

79% of clinic participants were female, compared to 46% for patients with KIT/PDGRA mutated GIST.
One patient has Carney's Triad, two patients have pulmonary chondromas, one has paraganglioma and one has NF1.

Clinical Course

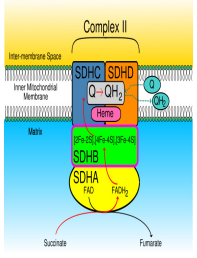
Average age at time of first symptoms	24.5 years	(range 5 – 58 years)
Average age at time of diagnosis	25.1 years	(range 5 – 58 years)
Current average age of patients	31.1 years	(range 12 – 63 years)
Average duration since time of diagnosis	5.5 years	(range 0 – 26 years)

	No evidence of Disease	Stable Disease	Progressive Disease	Deceased	Total
Children	5	3	1	1	10
Adolescents	4	3		1	8
Young Adults	6	4	4		14
Adults	1	4	2		7
Total	16	14	7	2	39

Overall survival rate is 95%. We expect to have sufficient follow-up data soon, to compare to adults with mutated GIST.

84% of patients presented with their primary disease located in the stomach.
11 patients had metastatic disease at the time of presentation (6 liver, 4 abdominal omentum, 2 lymph nodes, 3 other)
28 patients did not have metastatic disease, but 14 had multifocal disease (defined as multiple nodules in one organ)

Germline SDH Mutations



DNA nomemclature	Amino Acid change	Mutation type	Gene subunit	Clinical Course
c. 274 T>A/T	p. Ser 92 Thr	missense	SDH B	NED - 1st remission no therapy
c. 380 T>G	p. Ile 127 Ser	missense	SDH B	Never NED slowly progressive on TKI
c. 600 G>G/T	p. Trp 200 Cys	missense	SDH B	1st recurrence stable on TKI
c. 725 G>A/G	p. Arg 242 His	missense	SDH B	Never NED rapidly progressive on TKI
c. 405+1 G>A		splice site	SDH C	NED - 2nd remission no therapy
c. 34 G>A	p. Gly 12 Ser	missense	SDH D	NED - 1st remission no therapy
c. 34 G>A	p. Gly 12 Ser	missense	SDH D	1st recurrence partial response on TKI

The succinate dehydrogenase complex (SDH A-D) catalyses the oxidation of succinate to fumarate in the Krebs cycle
- the mutations occurred in all age groups (1 child, 2 adolescents, 3 young adults, 1 adult)
- the mutations occurred proportionally in both genders (5 females, 2 males)
- one patient has a complicated family history including GIST and paraganglioma in different family members
- no one has manifested any other tumors that are associated with SDH mutations, such as paragangliomas, pheochromocytomas, or renal cell carcinomas

We have identified germline SDH mutations in 7 (18%) of our clinic patients

Response to TKIs

	Complete Response	Partial Response	Stable Disease	Progressed	Discontinued Side Effects	Inevaluable	Taken Adjuvantly	Recently Started	TOTAL
Imatinib	0	1	1	20	3	3	6	0	34
HD Imatinib	0	0	3	2	2	1	0	0	8
Sunitinib	1	0	4	10	3	3	2	1	24
Nilotinib	0	0	1	2	0	0	0	6	9
Sorafenib	0	0	0	0	3	1	0	0	4
Dasatinib	0	0	0	0	1	0	0	0	1
TOTALS	1 (1%)	1 (1%)	9 (11%)	34 (42%)	12 (15%)	8 (10%)	8 (10%)	7 (9%)	80

36 patients have been treated with tyrosine kinase inhibitors
[12 patients received one agent, 11 received two agents, 9 received three agents, 3 received four agents, 1 received five agents]

The response rate to therapy with tyrosine kinase inhibitors is 19% and 2 patients had complete or partial response
[9 patients SD – Imatinib at 104 months, HD Imatinib at 28, 33, 91 months, Sunitinib at 8, 10, 18, 35 months, Nilotinib at 17 months]
[the response rate does not include those patients who were inevaluable, if taken adjuvantly, or if recently started]

The limited activity of TKIs in this population, compounded with its long duration of therapy, warrants a neo-adjuvant approach in patients with measurable disease

Patterns of Recurrence of GIST

15% of patients have never been free of disease **23% remain in first remission** **62% have recurred**

The recurrence rate is 73% **The average time to recurrence was 22.5 months (range 3 - 57 months)**
62% of patients had recurrence limited to one organ (6 abdomen, 5 stomach, 3 liver, 1 small bowel)
38% of patients had involvement of multiple organs (9 liver, 5 abdomen, 2 small intestine, 2 pelvis)

Of 24 patients who recurred, 13 have undergone a second surgery, but unfortunately 11 patients have recurred
The second recurrence rate is 85% **The average time to 2nd recurrence was 11.0 months (range 2 - 27 months)**

Two patients underwent total gastrectomy (one for second recurrence and one for third recurrence)
One patient remains disease free at three years, but the other patient recurred soon afterwards in the gastrectomy bed
Both patients had severe complications (nutritional deficiency, G-tube adjustments, abdominal pain, narcotic dependence)

Conclusions

The characteristics of patients with wildtype GIST are different from those with KIT/PDGFRA mutated GIST

- surgery alone has not been curative for recurrences in the majority of our patients (15%)
- response to tyrosine kinase inhibitors has been limited in our clinic population (19%)

Despite these findings, the majority of our patients are doing well (95% overall survival rate and 23% in first remission)

The participants of CPGR continue research efforts to identify the genetic changes that result in pediatric/wildtype GIST
Patients with GIST can greatly aid our efforts by participating in the NIH GIST clinic