Pediatric Gastrointestinal Stromal Tumors

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KEYWORDS

• Pediatric • Gastrointestinal stromal tumors • IGF-1 • Imatinib • Sunitinib • Carney triad

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract in adults.[1] These tumors are presumed to arise from the interstitial cells of Cajal and are characterized by the presence of activating mutations of the *KIT* or platelet derived growth factor receptor alpha *(PDGFRA)* proto-oncogenes.[1] The exact incidence of adult GIST is not known, but it is estimated that there are between 4000 and 5000 new cases in the United States annually. This figure reflects the results of population-based studies conducted in Sweden, Iceland, and the United States where the reported annual incidence for this tumor is 14.5, 11, and 6.8 cases per million population, respectively.[2–4] The median age at diagnosis is 60 years, and these tumors most frequently arise in the stomach (50%) and small bowel (25%).[5] Pathologically, 70% of adult GISTs are characterized by a spindle cell histologic subtype and 20% by an epithelioid architecture.[6] In adults, the determinants of malignant potential and clinical behavior include the stage at initial diagnosis, tumor size, mitotic rate, and anatomic location.[6] Activating mutations of *KIT* or *PDGFRA* are detected in over 90% of GISTs occurring in adult patients, and the majority of these patients respond to tyrosine kinase inhibitor therapy such as imatinib or sunitinib.[1,7,8]

GISTs rarely occur in pediatric patients, but increased recognition of adult GIST has led to better awareness of the existence of this entity in the pediatric population. GIST occurring in pediatric patients has a unique biology and clinical behavior and warrants discussion as an independent entity. The generally accepted definition of pediatric GIST is a tumor that is diagnosed at the age of 18 years or younger. This review highlights the clinical features, molecular biology, and clinical management of this rare pediatric entity.

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EPIDEMIOLOGY

The incidence of pediatric GIST in the United States is unknown, most likely owing to the relative rarity of the disease, the lack of consensus on how to code these tumors, the difficulties in separating malignant from benign tumors, and the diagnostic confusion that exists with other pathologic entities such as leiomyosarcoma, leiomyoma, or leiomyoblastoma.[9] A small number of series have estimated that pediatric GIST accounts for approximately 2.5% of all pediatric non-rhabdomyosarcomatous soft tissue sarcomas[10] or for 1.4% to 2.6% of all GISTs seen at large centers.[11,12] The Surveillance, Epidemiology and End Results (SEER) section of the National Cancer Institute data for GIST from 2001 to 2005 is depicted in **Table 1** and demonstrates that only 12 "true" cases of pediatric GIST were available for reporting during this period. Clearly, this figure underestimates the actual number of pediatric GISTs, and improved coding mechanisms and increased recognition of this entity are urgently needed to better define the incidence of this rare pediatric tumor.

ASSOCIATED CANCER PREDISPOSITION SYNDROMES

GIST can arise within the context of four well-defined tumor predisposition syndromes which need to be assessed at the time of initial evaluation of a pediatric patient with suspected GIST.

Table 1
Number of cases of gastrointestinal sarcoma reported to the SEER database, 2001–2005

	Study Period					
SEER 17 Areas (Age, y)	2001	2002	2003	2004	2005	2001–2005
00	0	0	0	0	0	0
01–04	0	0	0	0	0	0
05–09	0	0	1	0	0	1
10–14	1	2	0	2	0	5
15–19	1	2	1	1	1	6
20–24	3	1	0	2	1	7
25–29	2	9	4	7	4	26
30–34	7	14	6	5	6	38
35–39	15	15	20	15	16	81
40–44	21	29	23	25	27	125
45–49	34	37	30	33	45	179
50–54	29	57	39	51	42	218
55–59	27	58	62	62	63	272
60–64	43	45	53	51	49	241
65–69	48	66	62	53	46	275
70–74	61	55	65	67	55	303
75–79	48	59	56	52	36	251
80–84	30	39	44	37	36	186
85+	19	22	27	25	31	124
Total	389	510	493	488	458	2338

Carney Triad

In 1977, Carney reported the association of GIST, pulmonary chondroma, and functioning extra-adrenal paraganglioma.[13] Careful follow-up of these patients has revealed that they are at risk for other tumors as well, such as adrenocortical adenomas.[13] Most patients with the Carney triad are females (85%), and the mean age at presentation is 20.2 years; 82% present with clinical manifestations of this syndrome by age 30 years. Over half of the patients present with GIST and pulmonary chondroma, whereas 1% of patients present with pulmonary chondromas and paragangliomas without GIST.[13] GISTs in patients with the Carney triad tend to be multifocal and to arise in the stomach, particularly in the antrum and lesser curvature. Clinical presentation is often anemia due to gastrointestinal bleeding. Local recurrence (46%) and metastasis (55%) to the liver, lymph nodes, and peritoneum are not uncommon, but patients often have an indolent clinical course with recurrences reported as late as 39 years after initial surgery.[13] The Carney triad is sporadic; the underlying defect is not known, and GISTs in these patients lack *KIT*, *PDGFR*A, and succinate dehydrogenase (SDH) mutations.[14]

Carney-Stratakis Syndrome

Described in 2002, this syndrome is characterized by the presence of paragangliomas and GIST that are inherited in an autosomal dominant manner with incomplete penetrance.[15] The median age at presentation for these patients is 19 years,[16] and some patients can present with GIST, anemia, and gastrointestinal bleeding in the absence of a coexisting paraganglioma.[15,16] GISTs in these patients more commonly have an intramural and stomach location, exhibit spindle cell morphology, and are multifocal. *KIT* and *PDGFRA* mutations are absent,[16] but germline mutations or deletions in the genes for SDH B, C, or D are present in the majority of patients with the Carney-Stratakis syndrome as discussed later.[16,17] These patients also can have adrenocortical adenomas.

Familial Gastrointestinal Stromal Tumors

Germline mutations in *KIT* or *PDGFRA* have been reported in 14 families. The median age of diagnosis in patients with familial GIST is 46 years; therefore, this syndrome is less likely to be present in the pediatric population. Nevertheless, it is important to evaluate patients for signs and symptoms associated with *KIT* and *PDGFRA* germline mutations which include melanoma, lentigines, urticaria pigmentosa, perioral and perineal hyperpigmentation, and achalasia.[6,18]

Neurofibromatosis Type 1

The association between neurofibromatosis type 1 (NF-1) and GIST is discussed further in the review by Robson elsewhere in this issue. As is true for familial GIST, the median age of GIST diagnosis in NF-1 patients is younger than that observed in adult sporadic GIST (49 years) but outside the pediatric GIST age range.[6] Nevertheless, pediatric patients with GIST should be assessed for the presence of signs and symptoms of NF-1.

CLINICOPATHOLOGIC FEATURES OF PEDIATRIC GASTROINTESTINAL STROMAL TUMORS

The clinical characteristics, molecular findings, and pathologic features of 121 patients with pediatric GIST reported in 28 series or individual case reports are depicted in **Table 2**. The most common manifestations at the time of initial presentation included anemia or symptoms related to it, gastrointestinal bleeding, a palpable abdominal mass, abdominal distension, and intestinal obstruction, particularly in the newborn

Table 2
Clinical, pathologic, and molecular features of 121 pediatric patients with GIST reported in the literature

Study	Number of Patients, Age (y), Sex (F/M)	Location	Pathologic Subtype/Mitosis	Other Relevant Information	*KIT/PDFGR* Mutations	Imatinib or Sunitinib/ Evaluable Response	Outcome/Comments
Miettinen[11,a]	34 5–18 (median, 13) 27/7	Stomach (n = 34)[a]	Epithelioid (n = 21) Spindle/ epithelioid (n = 5) Spindle (n = 8) 0–65/50 (median, 6/50 HPF)	Size 1.5–24 cm (median, 6 cm) Carney's triad (n = 1) Multifocal (n = 1) Recurrence or metastases involving liver (n = 9)	None (n = 13)	N/A	NED (n = 21) 7–41 y AWD (n = 5) 9–22 y DOD (n = 6) 95% presented with anemia and gastrointestinal bleeding.
Janeway[20,b]	27 6–22 (mean, 14) 23/4	N/A	N/A	Carney's triad (n = 2)	None (n = 24) *KIT* V559-560 exon 11 (n = 1) *KIT* AY 502-503 exon 9 (n = 1) *PDGFR* D842V exon 18 (n = 1)	N/A	N/A
Agaram[19]	17 8–17 (median, 14.5) 12/5	Stomach (n = 15) Omentum (n = 1) Small bowel (n = 1)	Epithelioid (n = 8) Spindle/ epithelioid (n = 6) Spindle (n = 3) 1–76/50 HPF (median, 7)	Multifocal (n = 13) Carney's triad (n = 2) Peritoneal metastases (n = 9) Liver metastases (n = 5) Lymph node metastases (n = 4)	None (n = 15) *KIT* K557 exon 11 deletion (n = 1) *PDGFR* D842V exon 18 (n = 1)	Neoadjuvant imatinib (n = 6; 1 SD; 1 MR) Adjuvant imatinib (n = 1/NE) Sunitinib (n = 4; 1 SD; 1 MR) One patient received nilotinib with SD	NED (n = 6) 3–80 mo AWD (n = 8) 30–188 mo DOD (n = 1) 138 mo Mitotic activity did not correlate with clinical outcome. Mutations seen only in male patients.

Cypriano[10]	7 0.25–17 (median, 10.2) 4/3	Stomach (n = 2) Small intestine (n = 2) Colon (n = 2) Abdominal wall (n = 1)	Spindle (n = 5) Spindle/ epithelioid (n = 1) Epithelioid (n = 1) 5–250 mitosis/ HPF (median, 115/50 HPF)	Size <5 cm to 32 cm Local recurrence/ progression (n = 3) Liver metastases (n = 1)	N/A	Adjuvant imatinib/NE	4 NED 1.3–12.7 y
Price[22]	6 6–14 (median, 13.6) 4/2	Stomach (n = 6)	Spindle/ epithelioid (number not specified)	Carney's triad (n = 2) Multifocal (n = 3) Local recurrence (n = 1)	N/A (n = 3) No mutations (n = 2) *KIT* codon 456 exon 9 (n = 1)	N/A	NED (n = 4) Lost to F/U (n = 1) All patients presented with iron deficiency anemia and two had positive occult blood in stool. Endoscopic biopsies did not yield a diagnosis in these patients.
Kerr[44]	4 10–16 (median, 12) 4/0	Stomach (n = 4)	Spindle/ epithelioid (n = 4) 2–28 mitosis /HPF	Size 3.8–8 cm (median, 6.5 cm) Multifocal (n = 4) Lymph nodes (n = 2) Local recurrence (n = 1)	N/A	N/A	4 NED 8–9 y Three patients presented with anemia and gastrointestinal symptoms and one with a palpable abdominal mass.

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Table 2
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Study	Number of Patients, Age (y), Sex (F/M)	Location	Pathologic Subtype/Mitosis	Other Relevant Information	*KIT/PDFGR* Mutations	Imatinib or Sunitinib/ Evaluable Response	Outcome/Comments
Sauseng[47]	4 11, 13, 14, 16 3/1	Stomach (n = 4)	Epithelioid (n = 1) N/A (n = 3)	Carney-Stratakis (n = 1) Size 3.5–8 cm	N/A	Neoadjuvant imatinib (n = 1; 1 SD) Adjuvant imatinib (n = 1/NE)	NED 23 mo–10 y All patients presented with anemia, fatigue, and/or gastrointestinal bleeding.
Pasini[16]	2 9,13 0/2	Stomach (n = 1) N/A (n = 1)	N/A	One patient with multifocal disease Carney-Stratakis (n = 2) One patient a monozygotic twin	N/A	N/A	N/A
Muniyappa[48]	1 16 1/0	Stomach	Epithelioid	Size >6 cm Multifocal Liver metastases	N/A	Imatinib/PD	AWD 10 mo
Delemarre[25]	1 14 0/1	Stomach		Size 6 cm Liver and nodal metastases Carney's triad	No *KIT* or *PDGFR* mutations	Imatinib/1 PR	N/A

O'Sullivan[49]	1 11 1/0	Stomach	Spindle/ epithelioid <5/50 HPF	Size 3 cm Multifocal	No *KIT* or *PDGFR* mutations	N/A	NED 18 mo Patient presented with anemia and abdominal pain. Diagnosis was established by endoscopy.
Kuroiwa[21]	1 12 1/0	Stomach	N/A 8/50 HPF	Size 35 cm Multifocal	PDFGR codon 842 exon 18	Adjuvant imatinib/NE	NED 25 mo
Hayashi[50]	1 13 0/1	Stomach	Spindle/ epithelioid >5/10 HPF	Size 6 cm Liver metastases	N/A	Adjuvant imatinib/NE	NED 8 mo Patient presented with gastric bleeding and anemia.
Egloff[51]	1 8 1/0	Stomach	N/A	N/A	N/A	N/A	N/A Patient presented with gastrointestinal bleeding.
Iwasaki[52]	1 16 1/0	Stomach	Spindle <5/50 HPF	Size 7.5 cm	N/A	N/A	Unknown Patient presented with dizziness and anemia.
Chiarugi[23]	1 14 0/1	Duodenum	Spindle/ epithelioid <5/50 HPF	Size 4 cm	No *KIT* or *PDGFR* mutations	N/A	NED 24 mo Patient presented with anemia and upper gastrointestinal bleeding.

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Table 2
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Study	Number of Patients, Age (y), Sex (F/M)	Location	Pathologic Subtype/Mitosis	Other Relevant Information	*KIT/PDFGR* Mutations	Imatinib or Sunitinib/ Evaluable Response	Outcome/Comments
Park[53]	1 11 0/1	Stomach	N/A	Size 10 cm Multifocal	N/A	N/A	NED 9 mo Patient presented with abdominal pain and anemia.
Raffensperger[54]	1 14 1/0	Stomach	Epithelioid 1–2 mitosis/HPF	Size 4.5 cm Multifocal Liver metastases Lymph node metastases Carney's triad	N/A	Adjuvant imatinib/NE	DOD 16 y Patient presented with anemia, pallor, and fatigue.
Terada[55]	1 4 1/0	Colon	Spindle/ epitheliod 2 mitosis/10 HPF	Size 4.5 cm	N/A	N/A	NED 12 mo Patient presented with abdominal pain and constipation.
Wu[56]	1 0 0/1	Jejunum	Spindle <5/50 HPF	Size 3.5 cm	N/A	N/A	NED 12 mo Patient presented with abdominal distension and obstruction.
Mendes[57]	1 17 1/0	Stomach	Spindle/ epithelioid 4/10 HPF	N/A Carney's triad	N/A	N/A	NED 5 y
Bates[58]	1 14 d 1/0	Jejunum	1.5 cm Spindle and epithelioid 10/50 HPF	N/A	N/A	N/A	NED 12 mo Patient presented with intestinal obstruction.

Li[32]	1 12 1/0	Stomach	8 cm 5–6/50 HPF Epithelioid	8 cm Multinodular Liver metastases	No *KIT* mutations	N/A	Unknown Patient presented with anemia and diagnosis established by endoscopy.
Viola[59]	1 14 1/0	Small bowel	Spindle	Size 2.5 cm	N/A	N/A	NED 48 mo Patient presented with anemia and occult blood in stool. Diagnosis made by wireless capsule endoscopy.
Gallegos-Castorena[60]	1 12 0/1	Ileum	5 cm Spindle	Size 5 cm	N/A	N/A	NED 12 mo Patient had previous history of osteosarcoma and presented with abdominal pain and weight loss.
Shenoy[61]	1 newborn 0/1	Ileum	Spindle 1/10 HPF	2.5 cm	N/A	N/A	NED 12 mo Patient presented with abdominal distension and delayed passage of meconium.

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Table 2
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Study	Number of Patients, Age (y), Sex (F/M)	Location	Pathologic Subtype/Mitosis	Other Relevant Information	*KIT/PDFGR* Mutations	Imatinib or Sunitinib/ Evaluable Response	Outcome/Comments
Johnston[62]	1 17 1/0	Stomach	N/A	N/A	N/A	N/A	NED 13 mo Patient presented with anemia and a palpable abdominal mass, were unresponsive to preoperative chemotherapy with DTIC/doxorubicin, and had a previous history of neuroblastoma at 5 mo of age.
Murray[24]	1 15 1/0	Stomach	Spindle 1–2/10 HPF	N/A	No *KIT* or *PDGFR* mutations	Imatinib and sunitinib/SD	Unknown Patient presented with pallor, lethargy, and anemia.

Abbreviations: AWD, alive with disease; DOD, died of disease; F/U, follow-up; HPF, high power field; MR, mixed response; N/A, not available or not done; NE, not evaluable; NED, no evidence of disease; SD, stable disease.

[a] Included patients with gastric primaries only.

[b] This series included patients up to 24 years of age.

period. Two patients had a prior history of malignancy that included osteosarcoma and neuroblastoma. Twelve patients (10%) had a diagnosis of the Carney triad or Carney-Stratakis syndrome, emphasizing the need to search for features suggestive of these syndromes when initially evaluating pediatric patients with GIST. The GIST component of these syndromes usually presents with symptoms of anemia and gastrointestinal bleeding, whereas paragangliomas may elicit symptoms related to excess production of cathecolamines.[13,15]

Most patients with pediatric GIST present during the second decade of life; the median age at presentation in three large series was between 13 and 14.5 years.[11,19,20] Unlike adult sporadic GIST, pediatric GIST commonly affected females (89/121;74%), was associated with a higher proportion of tumors located in the stomach (79/93;85%), had a predominance of epithelioid (34/78;44%) or epithelioid/spindle cell morphology (22/78;28%), and rarely had *KIT* or *PDGFR* mutations. The reported tumor size varied widely (**Fig. 1**) and reached dimensions of up to 35 cm in one patient.[21] The mitotic rate ranged from 0 to 250; however, there was a lack of uniformity when reporting the number of high-power fields, which ranged from 10 to 50. In two series, the mitotic rate and the size of the tumor were not predictive of clinical behavior when adult reporting criteria were applied. These findings suggest that pediatric GIST has a somewhat unpredictable clinical course, and that patients may be more prone to have metastases regardless of the prognostic criteria used in adults, such as tumor site, size, and mitotic rate.[6,9,19,22] Another distinct feature of pediatric GIST is the presence of multifocality, which was reported in 28 of the patients (23%) depicted in **Table 2** and in 13 of 16 patients in one large series.[19] The presence of multiple tumor foci within an anatomic region may account for the high incidence of local recurrences as a result of incomplete tumor resection in these patients. The dramatic resemblance in clinical presentation, such as female predominance, multifocality, an indolent clinical course, and a lack of *KIT* or *PDGFR* mutations, between pediatric GIST and other syndromes such as NF-1, the Carney triad, and Carney-Stratakis dyad suggests that there might be a possible pathogenic link and requires further study.

PROGNOSIS

Pediatric GIST has an indolent clinical course. Despite the fact that many patients develop multiple disease recurrences spanning over many years or present with

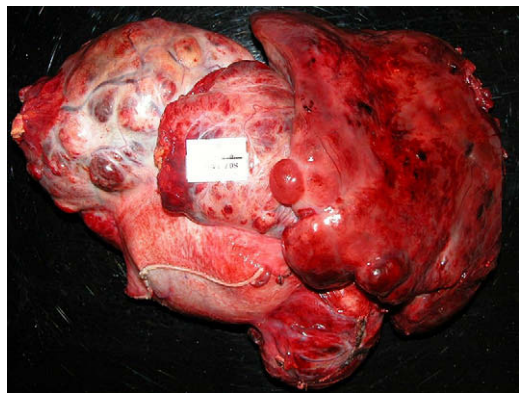

Fig. 1. Gross pathologic specimen of a large 10×7×5 cm GIST in a 9-year-old child. No *PDGFR* or *KIT* mutations were present in the resected gastric tumor. Despite the size, a complete resection was possible without compromising gastric function.

metastatic disease most commonly affecting the local tumor bed, lymph nodes, peritoneum, and liver, few have died of their disease. In one of the largest series of pediatric GIST reported to date, 10 of 12 patients (83%) had metastatic disease yet only one died as a consequence of this tumor.[19] Another large series with longer follow-up supports the assertion that pediatric GIST has an indolent course but also suggests that some patients will eventually succumb to the disease.[11] In this series, six patients died of disease after surviving a median of 16 years from the time of diagnosis.[11] These observations have important clinical implications for primary therapy, because extensive or disabling surgeries might not be indicated as a primary form of treatment for these patients (see management guidelines).

BIOLOGY OF PEDIATRIC GASTROINTESTINAL STROMAL TUMORS

Basic research on the biology of pediatric GIST has been hampered by the rarity of the disease and the lack of preclinical models. Despite these limitations, knowledge gained from the study of adult GIST and related tumor types (eg, paragangliomas) and the advent of newer research techniques (eg, expression and single nucleotide polymorphism arrays) have allowed for significant progress in the understanding of this rare and challenging pediatric entity.

Receptor Tyrosine Kinase Mutations

As mentioned previously, *KIT* and *PDGFRA* mutations are rare in pediatric patients with GIST. Among the 64 pediatric GISTs subjected to mutational testing and reported in the literature (**Table 2**), only 7 (11%) had a *KIT* or *PDGFRA* mutation.[11,19–25] Interestingly, these mutations were evenly distributed in exons 11 and 9 of the *KIT* proto-oncogene, and *PDFGR* mutations were relatively common, seen in three of the seven reported cases. This pattern is different from that seen in adults with sporadic GIST, in which *KIT* mutations are 10 times more common than *PDGFRA* mutations.[1] In pediatric GIST, these mutations are more often encountered in males. In fact, only one female patient aged less than 18 years with a *PDGFRA* mutation has been reported.[21] Although one could hypothesize that there are *KIT* and *PDGFRA* mutations in pediatric GIST that are located in different exons than those described in adults and are thus not sequenced in routine mutation analysis, no novel *KIT* mutations were identified when full coding length *KIT* sequencing from cDNA was performed in 11 pediatric GIST tumors.[19,20]

Genetic Mechanisms of Progression

Following receptor tyrosine kinase mutation, adult GIST undergoes a typical progression of chromosomal changes that can be detected by traditional cytogenetic analysis,[26,27] comparative genomic hybridization (CGH),[28–30] fluorescence in situ hybridization (FISH),[31] or single nucleotide polymorphism (SNP)[20] analysis. Similar chromosomal regions are affected in most adult GISTs regardless of whether the initiating receptor tyrosine kinase mutation is in *KIT* or *PDGFRA*.[26,29] The typically affected regions include 1p, 14q, 22q, and 9p,[26–31] and these chromosomal changes contribute to clinical progression. Loss of 14q and 22q loss is present in low- and high-grade GIST, whereas 1p and 9p loss occurs in more advanced GIST. Surprisingly, most pediatric GISTs lacking *KIT* or *PDGFRA* mutations (wild-type GIST) have minimal large scale chromosomal changes. By 10K SNP analysis, 12 of 13 pediatric wild-type GISTs had preservation of heterozygosity and diploid copy number throughout the entire genome.[20] Prior evaluations of GIST in pediatric patients using conventional cytogenetics have shown normal (diploid) karyotypes.[14,32] By CGH analysis, 60% of 13

wild-type GISTs occurring in pediatric patients with the Carney triad lacked chromosomal changes. Among the 40% of tumors with chromosomal changes, the most commonly identified abnormality was 1q deletion, seen in three GISTs; 1q contains the gene for SDHC discussed later.[14]

Gene Expression

In gene expression microarray experiments, pediatric wild-type GIST clusters distinctly from adult wild-type GIST and adult gastric GIST (95% of which have *KIT* or *PDGFRA* mutations).[19] GISTs occurring in young adults that have features similar to those seen in pediatric patients (multifocality, epithelioid morphology, and indolent course) have gene expression profiles that more closely resemble pediatric wild-type GIST.[19] Genes distinguishing pediatric wild-type GIST from adult wild-type GIST and adult gastric GIST include those for cytokine receptor-like factor 1 (CRLF1), fibroblast growth factor 4 (FGF4), brain and acute leukemia cytoplasmic (BAALC), pleomorphic adenoma gene 1 (PLAG1), and insulin-like growth factor 1 receptor (IGF1R).[19] The gene expression array experiments described previously were performed using a small number of tumor samples, and the results have not been confirmed by other groups due to the difficulty in obtaining fresh frozen samples suitable for RNA extraction in such a rare tumor.

KIT as a Potential Therapeutic Target

Although *KIT* generally lacks transforming mutations in pediatric GIST, it is expressed and activated in pediatric wild-type GIST.[19,20,33] Surprisingly, the extent of *KIT* activation in pediatric wild-type GIST is similar to that seen in adult *KIT*-mutant GIST.[19,20] The signaling intermediates downstream of *KIT*, mitogen activated protein kinase (MAPK), Akt, S6, and mTOR, are also activated in pediatric GIST.[19,20] These data suggest that *KIT* and downstream signaling intermediates may be reasonable therapeutic targets for pediatric patients with GIST. Small molecule inhibitors of *KIT* include imatinib (Gleevec), sorafenib (Nexavar), sunitinib (Sutent), nilotinib (Tasigna), and dasatinib (Sprycel). The potency of these molecules to inhibit wild-type *KIT* is not equivalent. When assayed in vitro in Ba/F3 cells stably expressing wild-type *KIT*, imatinib is the least potent with an IC_{50} of 3132 nmol/L, and nilotinib, dasatinib, and sorafinib are the most potent with an IC_{50} of 27, 44, and 66 nmol/L, respectively.[19]

Insulin-Like Growth Factor 1 Receptor

Expression of IGF1R is five times higher in pediatric wild-type GIST than in adult wild-type GIST.[19] The insulin-like growth factor 1 (IGF1) and its receptor, IGF1R, are central mediators of cellular growth and proliferation and normal growth and development as evidenced by the fact that mice lacking the IGF1R are half the size of normal mice.[34] An analysis of IGF1R protein expression in GIST by western blotting and immunohistochemistry shows that IGF1R is expressed in all GIST[35] but that levels of expression are much higher in wild-type GIST.[36] In the only published study of pediatric wild-type GIST in which IGF1R protein expression was evaluated, IGF1R expression was elevated to a similar degree as seen in adult wild-type GIST.[36] IGF1R is activated in most GISTs, but levels of activation do not correlate with the amount of total IGF1R expression.[36] High IGF1R expression in wild-type GIST is partially due to IGF1R gene amplification, which was present in 70% of wild-type GISTs and 30% of *KIT*/*PDGFRA*-mutant GISTs examined.[37] Importantly, during IGF1 stimulation, inhibition of IGF1R by a small molecule inhibitor decreased proliferation of a *KIT*-mutant GIST cell line, and co-administration of imatinib had an additive effect.[36] Braconi and colleagues[35] have also reported that IGF1 and IGF2 are variably expressed in GIST

and that higher levels of tumor IGF1 expression correlate with a poorer clinical outcome. These findings strongly argue in favor of pursuing the IGF1R as a therapeutic target in pediatric GIST.

Succinate Dehydrogenase and the Carney-Stratakis Syndrome

Germline mutations in the *SDHB*, *SDHC*, and *SDHD* genes are known to result in hereditary paragangliomas and pheochromocytomas,[37–39] and germline mutations or deletions in *SDHB*, *SDHC*, or *SDHD* are present in the majority of patients with the Carney-Stratakis syndrome.[16,17,40] Mutations or deletions involving *SDHB* are the most common, found in 4 of 9 families and 5 of 11 patients, followed by *SDHC* mutations present in 2 of 9 families and 2 of 11 patients, and *SDHD* mutations found in 1 of 9 families and 1 of 11 patients.[16]

Several recent reviews provide an in depth discussion of the mechanisms by which mutations in the genes for SDH lead to cancer susceptibility.[41,42] In hereditary pheochromocytoma and paraganglioma, SDH acts as a typical tumor suppressor gene.[41] In three GISTs from patients with Carney-Stratakis syndrome caused by germline SDH mutations, loss of the functional allele was documented, suggesting that SDH may act as a tumor suppressor gene in Carney-Stratakis syndrome associated with GIST as well.[16]

Whether SDH mutations are present in pediatric wild-type GISTs occurring in patients without an apparent family or personal history suggestive of Carney-Stratakis syndrome is an area of active research. An additional area of great interest is the extent to which SDH dysfunction is present in *KIT*/*PDGFRA*-mutant GISTs, GISTs arising in Carney triad patients, and adult wild-type GISTs. As mentioned previously, a subset of GISTs from patients with the Carney triad have deletion of the region containing *SDHC*.[14] *SDHB* maps to 1p36, and loss of 1p is relatively common in more advanced *KIT*/*PDGFRA*-mutant GISTs.[27,29–31] In a recent abstract, loss of heterozygosity at the *SDHB* loci was detected in 50% of GIST cases and loss of heterozygosity at the *SDHC* and *SDHD* loci were detected at a lower frequency.[43] Whether the genomic losses at *SDHB*, *SDHC*, and *SDHD* seen in *KIT*/*PDGFRA*-mutant GIST, adult wild-type GISTs, and GISTs arising in Carney triad patients are related to oncogenesis is not yet known.

EVALUATION AND WORK-UP

There are no published guidelines for the management of pediatric GIST, and the management guidelines herein are offered recognizing that, given the available published literature, recommendations are based on nonanalytic case series and expert opinion. **Fig. 2** summarizes the authors' suggested recommendations for the evaluation and diagnosis of these patients. Given its rarity and complexity, all children with suspected GIST should be managed by a team with expertise in sarcoma. Particular attention should be paid to the family history, prior history of malignancy, and symptoms of bleeding, anemia, abdominal pain, abdominal distension, hyperpigmentation, and catecholamine excess. Laboratory evaluations should include a complete blood count, reticulocyte count, and serum and liver chemistries. Initial anatomic evaluation of the tumor should include a chest radiograph (searching for pulmonary chondromas), a CT of the abdomen and pelvis, and, in selected cases, an endoscopy. Referral to an experienced surgeon preferably with expertise in the management of patients with sarcoma or GIST is recommended. Depending on the family history, they also may need to be assessed by an experienced geneticist.

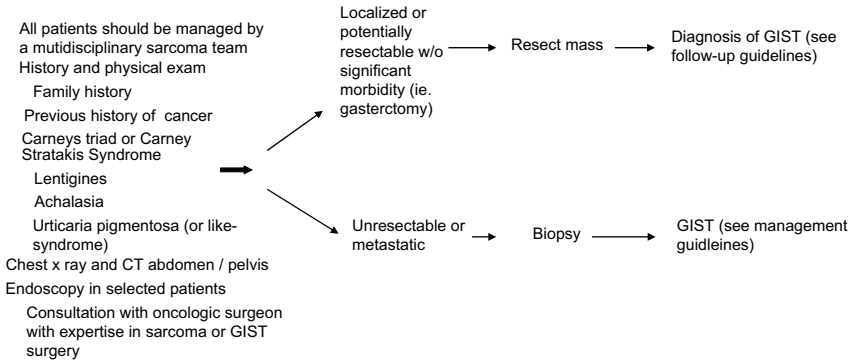

Fig. 2. Suggested guidelines for the initial evaluation of patients with pediatric GIST.

MANAGEMENT AND FOLLOW-UP

Once the diagnosis of GIST has been established, all samples should be subjected to mutational analysis (**Figs. 3** and **4**). If *KIT* or *PDGFR* mutations are detected, one should follow the guidelines published by the National Comprehensive Cancer Network for adult GIST (http://www.nccn.org/professionals/physician_gls/PDF/sarcoma.pdf). If no mutations are detected and the tumor is localized and resectable without significant morbidity (ie, total gastrectomy), surgical resection of the mass is recommended with the goal of achieving negative surgical margins. Although lymph node sampling is not recommended for patients with adult GIST, pediatric GIST is associated with a relatively high incidence of lymph node metastases;[19,44] therefore, any abnormal lymphatic chains identified at the time of surgery should be resected and submitted for pathologic examination. If all tumor has been resected, follow-up should include physical examination, a complete blood count, chest radiography, and CT of the abdomen and pelvis at

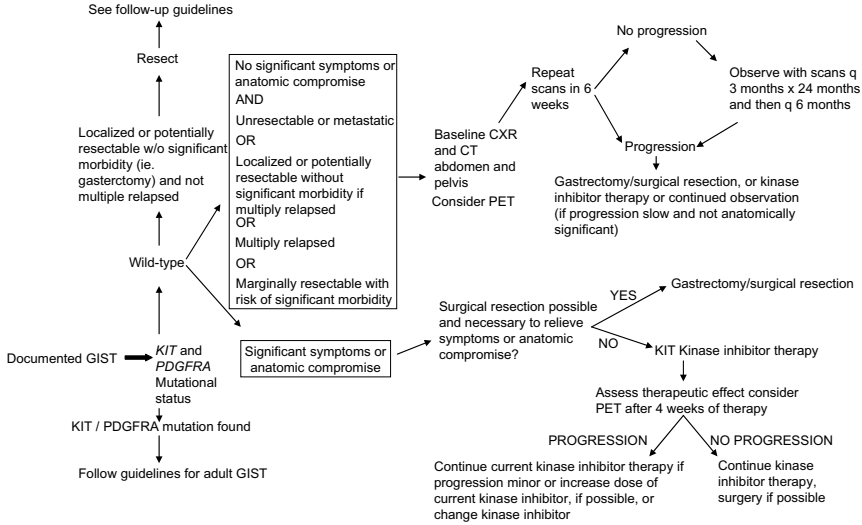

Fig. 3. Suggested management guidelines for pediatric GIST.

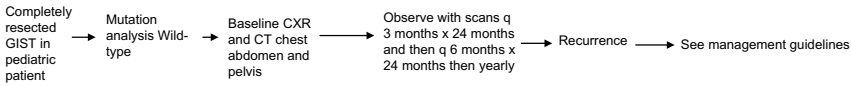

Fig. 4. Suggested follow-up guidelines for pediatric GIST.

3-month intervals for 24 months, followed by visits at 6-month intervals for 24 months and yearly thereafter.

For patients with unresectable or metastatic disease who are clinically asymptomatic, the authors recommend a set of baseline images including a chest radiograph and CT of the abdomen and pelvis and possibly positron emission tomography followed by repeat imaging in 6 weeks to assess the rate of tumor growth. If the patient is clinically stable and the tumor has remained stable in size, future imaging should follow the same intervals described previously. If significant progression develops at any time or the patient becomes clinically symptomatic, surgical resection of the primary tumor is recommended; if this is not feasible, institution of kinase inhibitor therapy should be promptly initiated. A similar management approach is recommended for patients with indolent multiply recurrent tumors who are asymptomatic and for those in which the initial results of surgical resection are expected to yield an incomplete resection or an inadequate functional outcome.

For patients who experience clinical symptoms or significant progression, the authors recommend surgical resection of the tumor even if it entails a total gastrectomy. If after consultation with an experienced surgeon it is apparent that surgical resection is not feasible, kinase inhibitor therapy should be initiated. It is not clear what the optimal front-line medical therapy should be for these patients. A review of 16 children and adolescents treated with various tyrosine kinase inhibitors is summarized in **Table 2**. Imatinib was administered in the neoadjuvant setting to 10 patients, with one partial response and three stable diseases observed. Sunitinib was administered to five patients with no significant objective responses; however, in a separate report not included in **Table 2**, Janeway and collaborators[45] described one patient with a partial response and five with disease stabilization that lasted from 7 to 18 months following the administration of sunitinib in seven patients who failed imatinib. Nilotinib was used in only one of patients, and the best response observed was stable disease.[19]

Based on these observations, the authors recommend imatinib as the first drug of choice to be used in the neoadjuvant setting at a dose of 230 mg/m^2 up to a maximum of 400 mg per day.[46] If future response assessment shows disease stabilization, this therapy and dose should be continued. If progression develops, an increase in the dose of imatinib to 600 or 800 mg per day (in adult-sized patients), a switch to another kinase inhibitor such as sunitinib or nilotinib, or enrollment in a clinical trial that incorporates novel treatments such as IGF1R inhibitors should be considered.

FUTURE RESEARCH

Much remains to be learned about the natural history, optimal management, and biology of pediatric GIST. The development of a registration trial with well-annotated samples is urgently needed to enhance our ability to study the biology of and develop more effective therapies for pediatric GIST. In an important step toward a national registration trial, the National Institutes of Health has recently developed an initiative to study pediatric GIST which includes a pediatric GIST clinic. This multidisciplinary clinic which convenes twice yearly brings together pediatric and adult oncologists, surgeons, and geneticists who carefully review and capture clinical and laboratory

information from significant numbers of pediatric patients with GIST. It is expected that this initiative will lead to a better understanding of the clinical and laboratory features of pediatric GIST. Priorities for biologic studies of pediatric GIST include the creation of a preclinical in vitro or in vivo model of the disease, further examination of the role of the IGF system in pediatric GIST oncogenesis, and evaluation of whether SDH mutations or other genetic alterations in SDH are present in pediatric GIST. Based on the laboratory observations described earlier, a phase II study of IGF1R monoclonal antibody therapy for pediatric wild-type GIST is being developed in collaboration with the Sarcoma Alliance for Research through Collaboration.

SUMMARY

Pediatric GISTs are different from adult GISTs and are characterized by female predominance, epithelioid histology, gastric location, a paucity of *KIT* or *PDGFRA* mutations, an indolent clinical course, and minimal response to tyrosine kinase inhibitors. Efforts to better study this disease are being undertaken and will likely lead to new treatment approaches for these patients.

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