Treatment Guidelines for Gastrointestinal Stromal Tumors in Children and Young Adults

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Summary: Gastrointestinal stromal tumor (GIST) occurring in the pediatric population has a unique biology and natural history when compared to GIST occurring in adults. As a result of these unique features, management of GIST in children may need to differ from management of GIST in adults. GIST is a very rare disease in children. Consequently prospective clinical trials have not been performed. A review of the biology, clinical presentation and natural history of GIST in children is presented. Guidelines for diagnostic evaluation and management of GIST in children are presented. The presented guidelines are based on clinical experience and data from case reports and case series.

Key Words: gastrointestinal stromal tumor, pediatric, child, succinate dehydrogenase

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Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumors of the gastrointestinal (GI) tract in adults and typically affect patients over the age of 40 years. However, this disease can occur in younger patients, albeit rarely. Children and young adults account for only 1.4% of patients with GIST. However, GIST has been reported in all age groups, including newborns.[1,2]

The 1992 to 2000 SEER data report an age-adjusted yearly incidence of 6.8 per million, 46% of whom were women and 54% men.[2,3] In a population-based study in Sweden, the annual incidence of GIST is estimated at 14.5 per million.[4] These figures may, however, underestimate the actual incidence of GIST and they likely represent the incidence in adult patients.

GIST originate from the myenteric ganglion cells (interstitial cells of Cajal) and were previously described in the literature as leiomyomas or leiomyosarcomas. GIST differs in gross morphology, ranging from minute nodules to large tumors. They can also differ in microscopic/histologic appearance. GIST may have predominantly spindle cells, epithelioid cells, or a mixture of both.[5] GIST occurring in pediatric patients tend to have an epithelioid morphology.[6] All but 5% of GIST express the membrane receptor tyrosine kinase CD117 (KIT). *KIT* gene mutations conferring constitutive activation occur in 85% to 95% of adult cases.[7,8] Approximately 5% of GIST occurring in adults have mutations in the platelet-derived growth factor receptor α (*PDGFRA*) gene.[2–3,9] Less than 15% of pediatric GIST have *KIT* or *PDGFRA* mutations; these tumors are often referred to as wild-type GIST (WT GIST).[10,11] The presence of tyrosine kinase mutations has prompted the development of large adult prospective trials using a variety of tyrosine kinase inhibitors such as imatinib or sunitinib with very favorable results.[12,13]

GIST can occur within the context of several cancer predisposition syndromes: Carney Triad, Carney-Stratakis Dyad, Neurofibromatosis type 1 (NF-1), and familial GIST. The Carney Triad is a sporadic syndrome defined by the association of GIST with paraganglioma, and pulmonary chondroma. The underlying genetic abnormality is not known. GIST in patients with Carney Triad tend to be multifocal and arise in the stomach, particularly in the antrum and lesser curvature, and they usually have an epithelioid morphology. Eighty-five percent of patients with Carney Triad are female, and the mean age at presentation is 20.2 years. Local recurrence (46%) and metastasis (55%) to liver, lymph nodes, and peritoneum are common but patients often have an indolent clinical course with recurrences reported as late as 39 years after initial surgery.[14] The Carney-Stratakis Dyad is an autosomal dominant inherited cancer predisposition syndrome caused by germline mutation in succinate dehydrogenase B, C, or D. Patients with the Dyad are predisposed to paragangliomas, GIST, and other tumors. GIST in these patients tend to be multifocal and located in the stomach and exhibit spindle cell morphology. The median age of presentation in these patients is 19 years.[15] More recently, the occurrence of germline mutations in succinate dehydrogenase B, C, or D has been described in pediatric patients with GIST who do not have a personal or family history of paraganglioma.[16] The familial GIST syndrome is due to autosomal dominant transmission of a constitutional, heterozygous, activating mutation in *KIT* or *PDGFRA*.[17] Those affected by the familial GIST syndrome usually do not present with a GIST until the mid-40s. In NF-1 patients, GIST are often small, multiple, mitotically inactive, clinically indolent with a predilection for the small intestine, with no *KIT*/*PDGFRA* mutations.[18]

Agaram et al[11] investigated 17 pediatric GIST cases for *KIT*/*PDGFRA* genotype and biochemical activation of the KIT downstream target. All 12 females in the study had tumors with a *KIT*/*PDGFRA* wild-type genotype distinctly different from the adult variant. However, 2 of 5 males showed activating *KIT*/*PDGFRA* mutations. Despite the lack of mutations in pediatric GIST, KIT is expressed and activated as signaling intermediates downstream of KIT.[10] An evaluation of 61 patients (including 15 children) with wild-type GIST identified *BRAF* mutations in 7% of adult GIST that lacked *KIT*/*PDGFRA* mutations. These *BRAF*-mutated GIST showed a predilection for the small intestine, and had a high risk of malignancy.[19] Recently, the insulin-like growth factor 1 receptor has been identified as being overexpressed in WT GIST including pediatric GIST. Insulin-like growth factor 1 receptor is another potential therapeutic target in this group of patients.[20]

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CLINICAL PRESENTATION

Although GIST may occur anywhere along the GI tract, the stomach (50%) and small intestine (25%) are the most common sites of occurrence. The colon (10%), omentum/mesentery (7%), and the esophagus (5%) are less common primary sites. A few may also occur within the abdomen and the retroperitoneum.[2,5] GI bleeding is the most common clinical presentation.[21] GI bleeding may be acute, presenting with hematemesis or melena, or may be chronic, presenting with anemia, weakness, and syncope, the latter presentation being the predominant one in children.[6,11] A study of 44 GIST diagnosed before the age of 21 years identified anemia secondary to chronic GI blood loss as the most frequent presentation.[6] Thus, GIST must be considered in the differential diagnosis of pediatric patients presenting with anemia secondary to GI blood loss. GIST may also present as an acute abdomen due to tumor rupture, with small or large bowel obstruction, or with abdominal pain or swelling. GIST can be completely asymptomatic, presenting as an incidental finding during surgery, radiologic studies, or endoscopy. This is especially true of smaller tumors and in environments where mass screening for gastric carcinoma is performed.[2,5] Advanced disease (in adults: 20% to 25% of gastric, 40% to 50% small bowel) usually manifests as liver metastases and/or dissemination within the abdominal cavity. Spread to other extra-abdominal sites such as the lungs and bones are uncommon. Lymph node metastasis is extremely rare in adults.[5]

GIST occurring in children have some distinct clinical and pathologic features. Pediatric GIST show a female predilection, whereas adult GIST do not. Multifocal gastric tumors and lymph node metastases are more common in pediatric patients. The histopathology is more likely to be epithelioid.[22] In a study of 15 patients younger than 30 years, all with WT GIST, pediatric GIST occurred more often in females, were more likely to present with multiple nodules in the stomach, and predominantly had an epithelioid morphology.[1] Similarly, a study of 44 cases of GIST occurring before the age of 21 years concluded that gastric GIST involving the antrum was common in children and that pediatric GIST were mainly epithelioid in morphology.[5] Among young adults, disease characteristics show a more heterogeneous pattern in that some bear the features of adult GIST, whereas others are more similar to pediatric GIST.[10,11]

NATURAL HISTORY

In adult patients, despite achieving complete resection in 85% of patients with primary tumors, the 5-year survival rate is 50%, with at least 50% of these patients subsequently developing recurrence or metastasis. The median time to recurrence after resection of a high-risk GIST is 2 years.[2,23,24] In adult patients with advanced GIST, before the advent of targeted tyrosine kinase inhibitor therapy, the median survival was 19 months.[25]

As a result of the rarity of pediatric GIST, precise estimations of progression-free and overall survival are difficult. Multiple disease recurrences and metastatic disease usually affecting the local tumor bed, lymph nodes, peritoneum, and liver are relatively common in pediatric GIST. Despite these features, pediatric GIST seems to have a more indolent course than adult GIST. In one of the largest series of pediatric GIST reported to date, 11 of 17 patients (65%) developed metastatic disease but only 1 patient had died.[11] Another large series with a 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. In this series, 6 patients died of disease after surviving a median of 16 years from the time of diagnosis.[6] These observations have important clinical implications for primary therapy.

DIAGNOSIS/STAGING

The diagnostic evaluation and work-up of pediatric patients with a differential diagnosis of GIST should involve a multidisciplinary team, preferably one with expertise in managing sarcomas or tumors of the GI tract. Components of the history and physical examination that should receive particular attention include family history, prior history of malignancy, symptoms of anemia and catecholamine excess, abdominal pain, abdominal distension, and the presence of skin findings associated with NF-1 and hyperpigmentation, which can be associated with familial GIST syndromes. A complete blood count, reticulocyte count, serum chemistries, and liver tests should be performed. Imaging studies should include at least a chest x-ray and abdominal and pelvic computed tomography (CT). Magnetic resonance imaging (MRI) may be an acceptable alternative to CT in some cases. For mucosal gastric lesions, endoscopy may be indicated. Concurrent imaging with CT and 18-fluorodeoxyglucose positron emission tomography (FDG-PET) may aid in the interpretation of CT findings, particularly where there is peritoneal disease.

The best approach for biopsy depends on the particular features of each case. An ultrasound-guided endoscopic biopsy is a possibility in patients with mucosal-associated gastric tumors.[2] Although preoperative biopsy of resectable masses is commonly performed to confirm diagnosis, it is not always necessary, and should be executed with care. GIST are fragile and soft, and so there is an associated risk of hemorrhage and tumor dissemination with biopsy.[1,2,6,26]

Several factors have been identified as conferring a poorer prognosis after complete resection of GIST in adult patients. These most important predictive factors are tumor size and mitotic activity.[7] These prognostic factors have not been validated in pediatric GIST. There is no specific staging system for pediatric GIST. The variable presence of *KIT*/*PDGFRA* mutations in pediatric patients and the implications of mutation status for treatment, discussed further below, make it imperative that all tumors be examined for mutations in these oncogenes.

Given the occurrence of germline mutations in the familial paraganglioma genes, succinate dehydrogenase B, C, and D, in some children with GIST without a personal or family history of GIST, referral to a genetic counselor is recommended for all pediatric patients diagnosed with a WT GIST (lacking a *KIT*, *PDGFRA*, or *BRAF* mutation).

MANAGEMENT RECOMMENDATIONS

Management should preferentially be by a multidisciplinary team, with expertise in sarcoma or tumors of the GI tract. The combined benefits of oncology, surgical oncology, pathology, and radiology in the initial evaluation, treatment, and follow-up of patients with GIST include optimal timing of surgical intervention and organ preservation, increased resectable cases by pharmacological debulking, reductions in recurrent disease, and prolonged survival.[2] Cytotoxic chemotherapy and radiotherapy are generally considered to be ineffective in GIST.[22]

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It is presumed that pediatric GIST carrying a *KIT* or *PDGFRA* mutation will have a similar natural history and therapy response as adult GIST. Thus, management recommendations for pediatric GIST depend on *KIT* and *PDGFRA* mutation status. If *KIT* or *PDGFRA* mutations are detected, it is suggested that the guidelines published by the National Comprehensive Cancer Network for adult GIST be followed.[2] The remainder of the management recommendations below pertains to WT GIST occurring in pediatric patients. There are no consensus guidelines for the management of pediatric GIST and there have been no prospective therapeutic treatment studies in this rare disease. The following recommendations are based on clinical experience and data from case reports and case series.

For initially diagnosed nonmetastatic resectable tumors, surgery is the mainstay of therapy. The goal of surgery is complete gross resection with an intact pseudocapsule and negative microscopic margins. It is recommended that all GIST be resected. Lymph node sampling, which is usually unnecessary in adults, may be considered in pediatric GIST patients who tend to have an increased incidence of nodal involvement. Recurrence can occur after total gastrectomy. Because gastrectomy and other extensive surgeries can have significant functional consequences and may not prevent recurrence, it is usually preferable to perform wedge resections. A more extensive discussion of surgical management of pediatric GIST can be found in a recent review.[27] Adjuvant imatinib is not recommended in pediatric patients with WT GIST because the available clinical data suggest that adjuvant imatinib might be less efficacious[28] and has not been adequately studied in this group of patients.

Because of the fact that pediatric GIST appears to have an indolent course and because there are no clearly efficacious treatments, patients with unresectable or metastatic disease who are clinically asymptomatic can be followed off therapy with frequent exams and imaging studies. A set of baseline images would include chest radiograph and CT (or MRI) of the abdomen and pelvis and, possibly, an 18-FDG-PET scan. Baseline imaging should be 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 intervals described below.

In patients with unresectable or metastatic disease who develop significant progression or clinical symptoms, surgical resection of the primary tumor should be performed if feasible. Ideally, surgical resection would be complete with negative margins. However, surgery should be considered even if it is not possible to achieve microscopic negative margins. The risks and benefits of surgery with significant functional consequences such as total gastrectomy should be weighed carefully on a case-by-case basis and in consultation with surgeons and oncologists familiar with GIST. If complete surgical resection is not feasible, institution of kinase inhibitor therapy should be promptly initiated.

For patients with multiple recurrent tumors who are asymptomatic, tyrosine kinase therapy should be considered.

Imatinib is the preferred front-line therapy in adults with advanced GIST because it prolongs the median survival from 20 to 57 months.[25,29] However, response to imatinib varies by tumor genotype. In adult patients with WT GIST, the objective response rate and median time to tumor progression with imatinib therapy are significantly lower than in adult patients with *KIT*/*PDGFRA* mutant GIST.[28] Sunitinib is 10 times more potent than imatinib with regard to inhibition of WT KIT.[11] In adult patients with advanced imatinib-resistant GIST, sunitinib significantly prolongs time to tumor progression and survival.[13] Sunitinib is approved multinationally for the treatment of adult GIST after disease progression on imatinib and is recommended for this purpose in the current clinical practice guidelines. Adult patients with WT GIST are among those achieving the greatest clinical benefit from sunitinib.[30]

It is not clear what the optimal front-line tyrosine kinase inhibitor therapy should be for pediatric patients. There are reports of imatinib administration in 10 pediatric patients. One partial response and 3 stable diseases were observed. Case reports of sunitinib administration to 5 patients show no significant objective responses.[22] In a more systematic study, sunitinib was administered in 7 patients who failed imatinib. There was 1 patient with a partial response and 5 with disease stabilization that lasted from 7 to 21 + months.[31] For imatinib, the pediatric dosing and adverse event profile are established.[32] A phase I trial of sunitinib in pediatric patients has been completed.[33] A phase II study of sunitinib in pediatric patients with GIST is ongoing. As there is no trial directly comparing imatinib and sunitinib in pediatric patients with GIST, it is not possible to know as to which agent should be used as the first-line therapy.

FOLLOW-UP RECOMMENDATIONS

These guidelines can be followed for completely resected tumors, asymptomatic unresectable, or metastatic tumors being followed off therapy (after the initial 6-wk interval), and patients on tyrosine kinase inhibitor therapy (after initial assessments every 6×12 wk).

Physical exam, complete blood count, chest radiograph, and CT (or MRI) of the abdomen and pelvis at 3-month intervals for 24 months followed by visits at 6-month intervals for 24 months and yearly thereafter is recommended.

SCREENING/PREVENTION RECOMMENDATIONS

Because of the extremely low incidence of pediatric GIST, routine screening is not recommended.

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