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Pediatric and wildtype gastrointestinal stromal tumour (GIST): new therapeutic approaches

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Abstract

Purpose of review—Pediatric gastrointestinal stromal tumor (GIST) is an uncommon tumor, the rarity of which has made both laboratory research studies and clinical management very difficult. As we learn more about this disorder, what is emerging is that this rare cancer is markedly different in children and adults. One of the main biological differences is that pediatric patients lack activating mutations in the oncogenes that drive tumor formation in adults. The natural history of this disease also appears to be more indolent in children than in adults. In this review, we will discuss the differences between children and adults with GIST and some new potential therapeutic agents.

Recent findings—This review discusses recent advances and the rationale for several recently identified molecular targets. In addition, we discuss the formation of a clinic at the National Institutes of Health that is dedicated to the study of this rare disorder.

Summary—Collaborative efforts are underway to better define the natural history and clinical course of pediatric patients with GIST. When combined with innovative genomic and molecular studies, these dual approaches will allow for notable advances in this field.

Keywords

Pediatric gastrointestinal stromal tumor; Molecular targeting; Rare disorders

INTRODUCTION

Gastrointestinal stromal tumor (GIST) is a rare mesenchymal tumor that affects approximately 4,000 people in the United States yearly. Prior to the demonstration of gain of function mutations in the KIT proto-oncogene twelve years ago, treatment for patients with this disorder was almost exclusively surgical [1]. The main determinants of survival in surgically resected patients are the size of the tumor, location and mitotic activity. Depending on the sum of these factors, disease-free survival (DFS) estimates can range from very poor to very good, approaching 90% 5-year DFS for those with a tumor in the stomach that is less than 5

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centimeters with less than five mitoses per 50 high-powered fields [2]. For patients with metastatic disease, despite aggressive surgical techniques, survival rates were abysmal since chemotherapy and radiation were largely ineffective in this disorder [3]. The identification of KIT and PDGFRA mutations in over 90% of adult patients with GIST has revolutionized the therapy of this disease [1,4]. Trials of Imatinib have shown safety and efficacy in patients with locally advanced and metastatic disease, and thus, therapy with Imatinib has become the standard of care for patients with unresected or metastatic adult GIST [5-7].

Pediatric GIST

Pediatric GIST is rare. Prevalence estimates are not available, but many series estimate that they account for only 1-2% of all sarcomas seen at large institutions [8-10]. The rarity of this disorder has prevented systematic clinical trials and the literature is comprised mainly of case reports or descriptive publications. However, these studies suggest that the biology of pediatric GIST is different from adult GIST. For example, patients with pediatric GIST are predominantly female, their tumors are of epithelioid or mixed histology, they lack large-scale chromosomal aberrations, and only rarely (< 15%) do they have KIT or PDGFRA mutations [11-13]. The natural history of pediatric GIST is also different. For example, despite multiple recurrences and lack of dramatic responses to tyrosine kinase inhibitor therapy, most patients survive with active disease for many years, suggesting a more indolent clinical course [10, 14-16]. Thus, based on our current knowledge, we can state that pediatric GIST is a relatively new and enigmatic entity that requires further study. However, the research that has been performed to date has revealed the following potential targets for therapy.

Targeting BRAF

Up to 13% of wildtype GIST, but not KIT/PDGFRA-mutated tumors, have been reported to harbor the V600E activating BRAF mutation [17-18]. Although this mutation is also linked with MAPK activation in many other tumor types, this does not appear to be the case in GIST [18]. Thus, it remains unclear if this event is responsible for driving tumorigenesis in wildtype GIST. Pre-clinical work in melanoma has validated V600E BRAF as a therapeutic target and specific BRAF kinase inhibitors, such as PLX4032, are currently being tested in clinical trials [19-20]. The involvement of a subset of GIST patients who have potential activation of this pathway, suggests that pediatric and wildtype GIST samples should be tested for the V600E BRAF mutation. Moreover, patients whose tumors have the mutation, and who have progressive disease, should enroll in a clinical trial that targets this pathway.

Targeting IGF-1R

The majority of wildtype GIST over-express the insulin-like growth factor receptor 1 (IGF-1R) compared to those from KIT/PDGFRA-mutated GIST [21-22]. One mechanism that accounts for this in a few samples is amplification of the IGF-1R locus, although for the majority of samples, the genomic mechanism that leads to over-expression has not been identified [21-22]. Modulation of the IGF pathway using IFG-1R kinase domain inhibitors in GIST cell lines derived from KIT-mutated tumors results in cytotoxicity, and specificity has been verified genetically using siRNA directed against IGF-1R [22]. These results support the hypothesis that GIST have activation of the IGF pathway and may thus be amenable to targeting. Recent studies have documented the efficacy and safety of monoclonal antibodies against IGF-1R, suggesting that this therapeutic strategy is a viable option in patients with wildtype GIST.

Targeting HIF-1a

A subset of younger patients who have GIST, also have paragangliomas, a syndrome known as Carney-Stratakis Syndrome [23]. These patients have germline mutations or deletions in subunits of the succinate dehydrogenase (SDH) gene, specifically in SDHB, SDHC or SDHD

[24-25]. Some paragangliomas and renal cell carcinomas also have SDH mutations, resulting in an increase in the downstream component, hypoxia inducible factor - 1 alpha (HIF-1a) [26]. Attempts to target HIF-1a have been under investigation for a variety of tumors types. For patients who have SDH mutations and HIF-1a over-expression, it is reasonable to consider targeting this pathway, using any one of many indirect methods that currently exist [27].

A paradigm for advancing pediatric and wildtype GIST

The biology of pediatric and wildtype GIST remains largely unknown, but the natural history suggests that new therapeutic approaches will be needed if we are to improve upon our current therapy. In order to increase our knowledge of this disorder and to increase the availability of tumor samples, the National Institutes of Health (NIH) initiated a clinic in 2008 to begin to address the limitations currently facing research and clinical care for patients with wildtype GIST. One goal was to determine the natural history of pediatric and wildtype GIST by bringing together patients with researchers and clinicians who study and treat GIST. Complete analysis of medical records, imaging studies and pathology results allowed us to assess the natural history of these patients and also the efficacy of different surgical techniques and medical treatments.

Top date, 50 patients with pediatric and wildtype GIST have attended four bi-annual clinics. Of those, 36% have the diagnosis of pediatric GIST (less than 19 years of age at the time of diagnosis). Patients ranged in age from 5 to 58 (average 26.3 years) at the time of their diagnosis and have had follow-up for an average of 5.9 years (range 0 to 35 years). The most pertinent findings from this clinic included: a predominance of female patients (70%), histology that was epithelioid or mixed epithelioid/spindled (70%), a vast majority with involvement of the stomach as the primary site (79%), and the presence of multifocal disease (56%). In addition, there was a very high recurrence rate (85%) and also a relative lack of efficacy using standard tyrosine kinase inhibitors (only 4% with a complete or a partial response). Despite these seemingly poor statistics, overall survival remained high at 96%, although follow-up was limited in some cases.

Forty percent of patients who attended the NIH Pediatric and wildtype GIST clinic have contributed tissue in the form of formalin-fixed paraffin-embedded tissue, either as blocks or unstained slides. We have utilized these samples to assess their eligibility for clinical trials and we will use any remaining samples for basic laboratory research. We plan to continue these clinics until all patients with pediatric or wildtype GIST have had an opportunity to attend.

From a clinical standpoint, we have the following objectives:

1. continue to gather information on the natural history of this rare disorder.
2. facilitate communication with referring physicians who are faced with difficult therapeutic questions when treating these patients.
3. determine which tyrosine kinase inhibitors or other experimental agents have been effective in treating this disorder.
4. assess patient eligibility for clinical trials.

From a research standpoint, we have implemented the following.

1. perform immunohistochemisty and mutational analysis of newly identified candidate genes.
2. look for changes in the following genes: BRAF, EGFR, HIF-1a, MET, NY-ESO, as potential candidates for targeted therapy.

3. obtain fresh frozen tumor sample for comprehensive genomic and proteomic testing, including sequencing of the transcriptome and entire genome.
4. establish cell lines at the time of surgery.

All of the patients who attended the NIH clinics were made aware of the types of samples that we wished to receive and the experiments that we could perform. Six patients underwent surgery after attending our clinic. Three patients underwent the procedure at institutions that were already equipped to perform the studies that we had planned. The other three patients requested that extra tumor be shipped to us, and we have received their frozen tumors. Matched normal/tumor DNA and RNA will be subjected to genome and transcriptome sequencing. A NIH GIST team member was also able to initiate a cell line at the time of one of these surgeries at an outside hospital and return it to the NIH for tissue culture. Initial results suggest that there are wildtype GIST cells growing in clumps, and our hope is that we will be successful in establishing a cell line from this sample.

CONCLUSION

Pediatric GIST research currently suffers from disadvantages that are common to many rare disorders, namely lack of reagents and resources. The NIH Pediatric and wildtype GIST Clinic is one means whereby we have started to overcome many of the obstacles that precludes the development of new and innovative therapies. In a span of only two years, we have quickly gathered data on many patients. We have also tested tissue samples to determine patient eligibility for clinical trials and performed laboratory-based studies. It is our belief that as more patients attend our clinics, that the number of samples will increase substantially. Researchers throughout the world, who are addressing novel questions, are welcome to make use of the samples that we have collected. We believe that a world wide collaborative effort will ultimately allow for rapid and prominent advances in the study and treatment of patients with pediatric and wildtype GIST.

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