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Neoadjuvant and Adjuvant Therapy for Gastrointestinal Tumors

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Abstract

Gastrointestinal tumors are the most common of a rare group of cancers known as mesenchymal tumors. New advances over the last several years have lead to the availability of targeted therapies in cancer and greater survival, particularly in this cancer type. This paper is a review of the current practices and treatments now utilized in the management of gastrointestinal tumors. Special emphasis was placed on treatment in Neoadjuvant and adjuvant settings. Research was conducted by inputting the words "GIST" "neoadjuvant", and "adjuvant" into the Cochran, Pubmed, and Ovid Database up to December 2013.

Keywords: Gastrointestinal tumor; Colon; Rectum; Esophagus

Introduction

In 1983, the term gastrointestinal tumor (GIST) was introduced by Mazur and Clark to define intra-abdominal tumors that were pathologically different from carcinomas and did not resemble either smooth muscle or nerve cells [1,2]. In the late 1990s, Sicar et al demonstrated that GIST tumor cells and the interstitial cells of Cajal (ICC), which are part of the myenteric plexus and operate to coordinate gut peristalsis, had common features, notably the expression of cKIT receptor tyrosine kinase (KIT RTK) [3], which suggests that the ICC cells may be the cell of origin for GIST tumor cells [4]. The identification of cKIT as a cell component of GIST tumor cells made it possible to pathologically distinguish this tumor from other GI sarcomas, which allows for a better diagnosis and estimation of its occurrence within our population [5].

Epidemiology

Prior to 2000 and the discovery of cKIT, the number of new GIST cases in the United States had been under diagnosed and therefore underestimated. With recent advances in understanding the biology and molecular pathogenesis of this tumor, differentiation of this tumor type from other gastrointestinal sarcomas has become more definitive. The estimated incidence of new cases of GIST arising in the United States annually is now believed to range between 3,000 and 8000 cases annually [6]. A population-based study to define the incidence of GIST using current criteria has reported an incidence of approximately 15 cases per million populations [7]. GIST occurs predominantly in adult men and women between 50-80 years of age, median age of 58 years, but it can occur across the age spectrum, with a slight male predominance [8]. The malignant potential of GIST neoplasm is quite varied. Forty percent of cases that are localized at presentation will become metastatic, and 10-20% of cases will present as metastatic disease [9].

Clinical Manifestations

GIST tumors may present anywhere along the GI tract. It occurs most frequently in the stomach (50%) and small intestine (25%), but cases of tumors located in the colon, rectum, and esophagus have also been reported [9]. About 10 percent of GISTs occur outside the GI tract but within the abdominal cavity and are referred to as extra-gastrointestinal tumors; these GIST locations are quite rare, and, when they do occur, they most frequently involve the omentum, mesentery, or retroperitoneum. The most common presenting symptoms of GIST are non-specific abdominal discomfort, nausea, early satiety, or GI bleeding. One third of cases are incidentally detected during imaging, screening or surgery for another reason.

Pathology and Diagnosis

GIST tumor morphology falls into three categories, spindle cell (70%), epitheloid (20%), or mixed (10%). The spindle cell GISTs are typically highly cellular tumors, often having an overall basophilic appearance because of high nuclear density and relatively scant cytoplasm. The epithelioid morphology is most commonly found in the stomach, omentum, and as disseminated intra-abdominal tumors of undefined origin. Epitheloid tumors are typically composed of polygonal cells with ample, amphophilic cytoplasm and round nuclei. The mixed morphology typically has features of the prior two categories [10].

The diagnosis of GIST is based on immunohistochemical staining for CD34 (myeloid progenitor cell antigen also present in GIST Tumor Cells) and CD117 (a cell surface antigen on the extracellular domain of KIT), in conjunction with pathological examination of tissue with light microscopy. Additional diagnostic criteria include inconsistent expression of smooth muscle actins (20-30%) and S100 protein (10%), and almost uniform negativity for desmin (only 2-4%) [11].

In 1998, two groups, Hirota et al. and Kindblom et al., showed through cellular and molecular studies the role of cKIT (a tyrosine kinase receptor) as a signal for cell proliferation and cell survival [3,12]. Both groups surmised that the interstitial cells of Cajal (ICC), found in the GI myenteric plexus, and GIST tumor cells appeared to have similar structural characteristics, including the expression of the

KIT protein, and that the major difference between the two types of cells was the KIT gain-of-function mutation. These studies were key in identifying the potential for neoplastic transformation in the event of a mutation in this transmembrane protein. Activation mutations in cKIT are now known to account for approximately 85 percent of GIST Tumors. Mutations in KIT generally occur in the juxta membrane domain encoded by exon 11. Other exons where mutations are typically found include 9, 13 and 17. A mutation in exon 9 is most often linked to tumors that arise in the small intestine or other non-gastrointestinal sites and are typically resistant to treatment with Imatinib. Mutations in exon 17 are usually associated with primary resistance to Imatinib, and mutations in exon 13 in patients not exposed to Imatinib are associated with prolonged responses with Imatinib use [13].

Approximately 15 percent of GIST patients do not demonstrate activational mutations of the KIT receptor [14]. In 2003, Hirota et al. described another gain in function mutation in the platelet-derived growth factor receptor, alpha polypeptide (PDGFRA), in KIT negative GIST Tumors [15]. PDGFRA accounts for 10 percent of all GIST. Tumors with this mutation tend to be located in the stomach and the omentum and have varying responses to treatment with Imatinib. The most common mutations of PDGFRA are in exons 18, 12, and 14 [16].

Roughly 5 percent of GISTs will have no detectable kinase mutations and are often referred to as wild type GIST. A large number of wild type GISTs are associated with deficiencies in succinate dehydrogenase (SDH); however, other mutations have been identified, such as alterations in the neurofibromatosis (NF1) gene, activational mutations in BRAF oncogene, RAS–family mutations, as well as familial syndromes such as Carney-Stratkis, Carney's triad, and Familial GIST, have all been associated with the development of GIST tumors [17-19].

Therapeutic Options for GIST Management

Surgical Resection

The mainstay of therapy for GIST is complete macroscopic surgical resection with negative microscopic margins of >2 cm (R0 resection). A complete resection of gross tumor may require visceral resection, omentectomy, and peritoneal stripping. Because metastatic disease in the liver is usually multifocal and may not be amenable to segmental or lobar hepatectomy, radiofrequency ablation or hepatic embolization may need to be performed. Even with a R0 resection, historical data suggests that the median time to recurrence is usually between 19-25 months, with an overall 5-year survival rate of less than 50 percent [9,20]. Recurrences frequent the liver, peritoneum, or abdomen. Given this high rate of recurrence, the ability to evaluate a patient's risk of recurrence and the benefit of adjuvant therapy after surgery is necessary.

Risk Stratification

There are three commonly utilized risk stratification models: (1) the Armed Forces Institute of Pathology (AFIP) Criteria; (2) the Modified NIH Joensuu Criteria; and (3) the National Institute of Health (NIH) Fletcher Consensus Criteria [21-23]. All three models were validated by Brian et al. in 2008. The tumor characteristics assessed in these models are large tumor size, high mitosis count, non-gastric locations, presence of rupture, and male sex. Patients at high risk for recurrence usually include patients whose tumors are larger than five centimeters in diameter and contain over five mitoses/50 high power fields; patients presenting non-gastric GISTs larger than five centimeters in diameter; and patients whose tumors are smaller than five centimeters with a mitotic count exceeding 5/50 [24]. The NCCN has modified the AFIP table to include tumor location as a factor affecting risk of recurrence. Patients who were identified as intermediate risk had a clinical course that was similar to the low-risk group, suggesting that only high-risk patients would likely benefit from adjuvant therapy. As patients labeled as very low, low, or intermediate risk have minimal benefit from adjuvant therapy it is usually not offered in this setting (Table 1-2).

AFIP Criteria			
Risk Group	**Diameter**	**Mitoses Count**	**10 year RFS**
Group 1	<2.0	≤5	95.0
Group 2	2.1-5.0	≤5	89.6
Group 3a	5.1-10.0	≤5	79.7
Group 3b	>10.0	≤5	61.9
Group 4	<2.0	>5	45.7
Group 5	2.1-5.0	>5	48.9
Group 6a	5.1-10.0	>5	25.1
Group 6b	>10.0	>5	9.4
NIH Consensus Criteria			
Very Low Risk	<2	<5	98.3

Low Risk	2-5	<5	88.2
Intermediate Risk	<5 5-10	6-10 <5	79.8
High Risk	>5 >10 Any Size	>5 Any count >10	30.4
NIH Modified Risk Stratification Criteria			
Very Low Risk	<2.0	≤5	94.9
Low Risk	2.1-5.0	≤5	89.7
Intermediate Risk	≤5.0 5.1–10.0	6–10 ≤5	86.9
High Risk	>10.0 Any size >5.0 ≤5.0 5.1–10.0 Any size	Any count >10 >5 >5 ≤5 Any count	36.2

Table 1: AFIP Criteria [39]

NCCN Risk Stratification					
Mitotic Index, HPF	**Size, cm**	**Site and Risk Group (Risk of Progression %)**			
		Gastric	**Duodenum**	**Jejunum/Ileum**	**Rectum**
≤5 per 50	<2.0	None (0)	None (0)	None (0)	None (0%)
	2.1–5.0	Very Low (1.9)	Low (4.3)	Low (8.3)	Low (8.5)
	5.1–10.0	Low (3.6)	Moderate (24)	Insufficient Data	Insufficient Data
	>10.0	Moderate (10)	High (54)	High (34)	High (57)
>5 per 50	<2.0	None (0)	High[a]	Insufficient Data	High (54)
	2.1-5.0	Moderate (16)	High (73)	High (50)	High (52)
	5.1-10.0	High (55)	High (85)	Insufficient Data	Insufficient Data
	>10.0	High (86)	High (90)	High (86)	High (71)

Table 2: A Small number of cases [40]

Adjuvant Imatinib

cKIT and PDGFRA belong to a family of receptors known as tyrosine kinase receptors, which have been shown to play critical roles in a variety of cellular processes, including growth, differentiation, and angiogenesis. Mutations in these receptors result in their constant activation, which leads to increased cell longevity and tumor development. The discovery of these receptors and the identification of their mutations as driving cause of GIST tumor development led to rapid progress in the management of this illness. Historical data show that management of GIST prior to 2000 involved surgery, in some cases radiation, and utilization of the same chemotherapeutic agents used to manage sarcoma, to which GIST tumors were largely resistant [25]. In 2001, Imatinib, a selective inhibitor of the tyrosine kinase receptor BCR-ABL that binds to it and prevents it from stimulating cellular growth, was approved for the treatment of Chronic Myelogenous Leukemia. Its approval was shortly followed by the publication of a single case report in the New England Journal of Medicine, which showed durable response in a patient with metastatic GIST [26]. This case report led to multiple phase II and III trials demonstrating the effectiveness of Imatinib in the metastatic setting. Based on these favorable results, trials were conducted to explore the potential use of Imatinib in the adjuvant setting for primary GIST.

Adjuvant therapy with Imatinib for gastrointestinal stromal tumors has been evaluated in multiple trials (Table 3). ACOSOG Z9000 was a

single arm phase II trial that determined that use of Imatinib as adjuvant treatment for one year in patient at high risk for recurrence (incomplete idea?). 107 patients with completely resected GISTs ≥10 cm in size, ruptured, hemorrhaging, or multifocal GISTs (<5 sites total) received 400 mg Imatinib daily for one year. Recurrence-free survival (RFS) was the primary endpoint. At a median follow-up of 7.7 years, the one-, two-, and three-year overall survival rates were 99, 97, and 83 percent, respectively, and the corresponding rates of RFS were 96, 60, and 40 percent, respectively [27].

Study (Ref.)	# Enrolled	Intervention	Results
ACOSOG-Z-9000 (DeMatteo RP B. K., 2013) phase II prospective single arm	107	Adjuvant imatinib; 400 mg/day for 1 year	OS-1 year 99 %, 3 years 97 %; RFS-1 year 94 %, 3 years 61 %
AMC-ONCG1-0501(Kang B, 2009)(41); phase II prospective Randomized	47	Adjuvant imatinib; 400 mg/day until progression/ toxicity, or 2 years	RFS—1 year, 98 %; 2 years, 93 %
ChiCTR-TCC00000582 (Li J, 2011)[42]; phase II Double blind randomized	105	Imatinib or placebo/400 mg Daily for 36 months	RFS Imatinib vs. placebo Year 1 – 100 % vs. 90 % Year 2 – 96 % vs. 57 % Year 3 – 89 % vs. 48 %
Kang et al ; Phase II Single arm (Kang B, 2009)	47	Imatinib for 2 yrs or until progression	RFS- 2 years 93 %
ACOSOG-Z9001 (DeMatteo RP B. K., 2009) ; phase III prospective randomized	713	Adjuvant imatinib; 400 mg/day for 1 year	1 year RFS; imatinib 98 %; placebo 83 %
EORTC 62024; Phase III prospective, randomized	908	Adjuvant Imatinib 400 mg vs. observation for 2 years or until progression	Imatinib failure-free survival 5 year 87% vs. 84% RFS 3-year 84 vs. 66 % OS 5-year 100 vs. 99 %
SSG XVIII/AIO trial (Joensuu H E. M., 2012); Phase III prospective randomized	400	Adjuvant Imatinib, 400 mg per day, orally for either 12 months or 36 months, started within 12 weeks of surgery	RFS 5-year 65.6% (36 months) vs. 47.9% (12 months) OS 5-year 92.0% (36 months) vs. 81.7% ((12 months)

Table 3: Studies on Adjuvant Use of Imatinib

This study was followed by the landmark ACOSOG Z9001, a double blind phase III trial which randomized 713 patients with localized resected GIST (whose lesions were >3 cm) to receive either Imatinib or placebo for one year. After a median of 15 months follow-up, only 3 percent of patients who received one year of Imatinib after surgery exhibited a recurrence of GIST, compared with a 17 percent recurrence rate in patients who received the placebo. The one-year RFS rate was 98 versus 83 percent favoring Imatinib, with a hazard ratio for RFS of 0.35, 95 percent CI 0.22 to 0.53. Long-term analysis suggests an absolute benefit in those with high-risk disease (relapse rate 47 versus 19 percent for placebo and Imatinib, respectively). This study confirmed benefit in using Imatinib as adjuvant therapy in patients who are at high risk for recurrence of GIST [28].

One question left unanswered by Z9001 was duration of adjuvant therapy. EORTC 62024 randomized intermediate and high-risk GIST patients after R0-1 resection, to receive Imatinib 400 mg daily vs. placebo for 2 years or until disease progression/unacceptable toxicity. The original primary endpoint was overall survival; however, in 2009, the endpoint was changed to Imatinib-free survival (IFS, the time to death or starting a TKI other than Imatinib). In a preliminary report at ASCO 2013, after a medial follow up of 4.7 years, five-year IFS was 87 percent in the Imatinib arm, compared to 84 percent in the control arm (HR 0.80, 95% CI 0.51-1.26); three-year RFS was 84 versus 66 percent; and five-year overall survival was 100 versus 99 percent. In patient with high-risk GIST, there was a trend towards improved IFS that favored adjuvant Imatinib (five-year IFS 77 versus 73 percent, p = 0.44).

Joensuu et al. also addressed that question in SSG XVIII, a randomized control study comparing the use of Imatinib as adjuvant therapy for one year versus three years. They randomized 397 high-risk patients to receive either 36 months or 12 months of Imatinib as adjuvant therapy after surgery. High risk was defined as (i) tumor diameter >5.0 cm and mitotic count >5/50 high power fields (HPFs); (ii) tumor diameter >10.0 cm with any mitotic count; (iii) tumor of any size with a mitotic count >10/50 HPFs; or (iv) tumors ruptured into the peritoneal cavity. Results from that study showed a benefit to prolonged use with an RFS of 65.6 percent compared to 47.9 percent after five years. This translated into a difference in overall survival, with a hazard ratio of 0.45 in the group receiving three years of Imatinib [29]. After stopping the drug, both groups were noted to have a rapid recurrence of disease, suggesting that even 3 years may not be

the optimal length of time needed for suppressing disease recurrence [30].

In 2008, the FDA granted accelerated approval for Imatinib in the adjuvant setting for completely resected primary GIST ≥3 cm, without indicating the optimal length of therapy. Labeling was updated in January 2012 to include the significantly prolonged survival seen with three years of therapy as compared to one year of adjuvant Imatinib. However, whether all patients in this broad category have a high enough risk of recurrence to warrant adjuvant therapy has not yet been established. The EMA (European Medicines Agency) has extended the licensed indications of Imatinib to include adjuvant treatment of adult patients who are at "significant risk of relapse" after resection of a KIT-positive GIST, but does not further define these subsets. Consensus-based clinical practice guidelines from the National Comprehensive Cancer Network (NCCN) suggest adjuvant Imatinib for at least 36 months for patients with high-risk GIST (tumor >5 cm in size with high mitotic rate [>5 mitoses/50 HPF], or a risk of recurrence >50 percent). The proposed, modified NIH criteria identify a single subgroup of patients at high risk of recurrence. Patients who were identified as intermediate risk had a clinical course that was similar to the

only the high-risk patients would likely benefit from adjuvant therapy. Based upon these data, it would seem reasonable to offer adjuvant therapy for at least three years to all patients who fall into a “high-risk” category, regardless of the risk stratification model used. Duration of treatment beyond that time remains unclear.

Imatinib is generally well tolerated. The most common adverse effects reported include edema, cough, night sweats, rash, weight gain, nausea, vomiting, diarrhea, fatigue, headache, and myalgias/arthralgias. More serious side effects include cardiac tamponade, heart failure, cytopenias, renal failure, cerebral edema, liver failure, and secondary malignancies [31].

Resistance to Imatinib

During the trials evaluating Imatinib for the management of unresectable/metastatic disease a population was identified to have primary resistance to Imatinib [26]. In addition, there was also a small subset of patients in the adjuvant setting that developed a secondary resistance to Imatinib therapy. Resistance to Imatinib both primary and secondary begins with mutations in KIT/PDGFRA. Data reported by Joensuu and colleagues [29] and Z9001 showed that patients with KIT exon 11 mutations benefit the most from prolonged adjuvant treatment. Primary resistance has been linked to mutation in PDGFRA exon 18 p.D842V which alters the binding ability of Imatinib. Treatment with Imatinib is not recommended in patients with this mutation. Another treatment related mutation is in KIT exon 9. Studies suggest that patients with this mutation do not benefit from routine dosing of 400 mg daily and may need a dose increase to 800 mg daily to benefit from treatment with Imatinib [32].

Neoadjuvant use of Imatinib

Patients with locally advanced and unresectable GIST have a survival rate that is comparable to those patients with metastatic disease. The goal of neoadjuvant imatinib therapy in GIST is to improve the survival of surgical candidates at risk for high morbidity with locally advanced tumors, to increase the chances of obtaining an R0/R1 resection in patients with large tumors, and to make unresectable tumors operable. Neoadjuvant therapy is not indicated in patients with tumors classified as very low or low risk. The efficacy of imatinib as neoadjuvant therapy was first reported by Bumming et al (2003) as a case report of a 56 year old man who presented with a 35 cm tumor with 6 liver metastasis who received 12 weeks of Imatinib and saw complete resolution of his liver metastasis and a reduction of his primary tumor to 18 cm. Patient was then resected with good margins [33]. After the publication of this case report, several other dramatic responses leading to the ability to completely resect tumors initially considered unresectable were reported.

In 2009, Hohenberger et al. conducted a trial where they treated 33 patients with locally advanced GISTs with 11 months of neoadjuvant Imatinib. The results were a reduction in tumor size, improved morbidity, and five patients whose tumors were thought to be unresectable became resectable [34]. Shortly after, the RTOG (Radiation Therapy Oncology Group) 0132/ACRIN (American College of Radiology Imaging Network) 6665 trial was conducted. RTOG 0132 was a prospective phase II trial which included 30 patients with primary GIST with KIT-positive GIST and either a resectable primary ≥5 cm, or resectable recurrent disease. The Intervention was preoperative Imatinib 600 mg daily for 8 to 12 weeks, with at least two more years of adjuvant Imatinib post surgery. Two-year progression-free survival for patients with resectable disease was 83 percent, and estimated overall survival was 93 percent. In 2011, Blesius et al. conducted a subgroup analysis of BRF14 and were able to isolate 25 patients who had no metastatic disease at the time of inclusion in the trial. After a median of 7.3 months of treatment with Imatinib, 36 percent of these patients were able to undergo resection of their primary tumor, and their OS and PFS figures were close to those of localized intermediate or high-risk GIST [35] (see table 4). More recently Rutkowski et al. conducted a pooled analysis of 10 EORTC and STBSG sarcoma centers and were able to identify 161 patients with locally advanced GISTs who received neoadjuvant Imatinib for a median time of 40 weeks. Eighty three percent of these patients were able to undergo an R0 resection, only two patient progressed while on neoadjuvant therapy. Fiver year disease free survival was 65 percent and median overall survival was 104 months. The data supports preoperative use of imatinib for selected patients with locally advanced or marginally resectable tumors [36].

Study (Ref.)	#Enrolled	Intervention	Results
MDACC ID 03-0023 (McAuliffe JC, 2009)[43]; phase II prospective randomized	19	Neoadjuvant-600 mg/day,3, 5, or 7 days; adjuvant- 600 mg/day, 2 years	DFS- 1 year, 94 %; 2 years,87 %

RTOG-S01/ ACRIN 6665 32 (Eisenberg BL H. J., 2009)[44]; single arm/ nonrandomized II prospective study	52	Neoadjuvant-600 mg/day, 8-12 weeks; adjuvant- 600 mg/day, 2 years	PFS at 2 years, 77-83 %; OS at 2 years, 91-93 % PFS at 5 years localized 57% vs. metastatic 30% DFS at 5 years localized 77% vs. 68 % metastatic

Table 4: Prospective Studies on Neoadjuvant Use of Imatinib

Evaluation of Response to Neoadjuvant Therapy

Preoperative treatment with Imatinib is recommended in patients with resectable tumors that have a high risk of morbidity due to the extent of the surgery, as well as patients whose lesions are only borderline resectable. Close monitoring during neoadjuvant therapy is highly recommended, as a patient can quickly progress and become unresectable. Timing and frequency of reassessment have not clearly been defined through clinical trials, but recent data suggest that short interval PET CT is capable of showing metabolic response of tumor to Imatinib and should therefore be utilized initially to assess response to neoadjuvant treatment [37]. Currently the NCCN suggests that patients should be imaged every 2-4 weeks while on neoadjuvant therapy, until the imaging reveals a maximum response which is defined as two consecutive scans not showing progression or a scan that shows a lesion that is surgically resectable.

Future Directions

Sunitinib mesylate, a multi-target oral tyrosine kinase inhibitor, and Regorafenib, an oral multikinase inhibitor targeting VEGF receptors, KIT, PDGF receptors, and FGF receptors have both been approved by the FDA in the setting of advanced disease, but no trials are ongoing to evaluate them in the neoadjuvant or adjuvant setting.

Further ongoing research involves testing newer TKIs as single agents and in combination with other targets along the activation pathway, such as inhibitors of phosphatidylinositol 3-kinases (PI3K), the mammalian target of rapamycin (mTOR), and the mitogen-activated protein kinase (MAPK) pathway (Table 5).

Study	Patient Characteristics	Intervention	End Point
NCT00867113; Phase II, non-randomized, open-label, multi-center	Patients at significant risk for recurrence following complete resection of primary GIST.	Imatinib mesylate 400 mg once per day by mouth for 5 years.	Time to Recurrence Safety and Tolerability
NCT01054911; Single institution, nonrandomized open label study		Sunitinib 37.5 mg p.o. daily for up to 12 weeks followed by surgical resection	Safety and efficacy RR

Table 5: Current Adjuvant/Neoadjuvant Clinical Trials Ongoing in GIST [45-50]

TKIs currently being evaluated include Dasatinib, an oral multi-BCR/Abl and Src family tyrosine kinase inhibitor; Dovitinib, a receptor tyrosine kinase (RTK) inhibitor targeting vascular endothelial growth factor receptors, fibroblast growth factor receptors, and platelet-derived growth factor receptor; and Masitinib, an inhibitor of cKit PDGFR, and fibroblast growth factor receptor (FGFR). Other targeted therapies in trial in patients with advanced disease include (i) HPS90-inhibitors AUY922 and BIIB02, which promotes degradation of KIT; (ii) Palbociclib, a selective inhibitor of the cyclin-dependent kinases CDK4 and CDK; (iii) Crenolanib, a selective and potent inhibitor of type III receptor kinases FMS-like Tyrosine Kinase 3 (FLT3) and PDGFR; and (iv) Lisitinib, an inhibitor of the insulin receptor and the insulin-like growth factor 1 receptor (IGF-1R) [38].

The agents that prove to be effective during these trials may be considered for future use in the neoadjuvant and adjuvant settings. As the molecular pathogenesis of this disorder is more clearly defined, more effective therapies will continue to be added to the treatment of GIST.

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