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Review

Current management of gastrointestinal stromal tumors – A comprehensive review

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ABSTRACT

Background: Gastrointestinal stromal tumors (GISTs) comprise < 1% of all gastrointestinal (GI) tumors, but GISTs are the most common mesenchymal tumors of the GI tract. Dramatic changes in clinical practice have been observed in the last decade. This review highlights the overall management of GIST and its recent developments.

Method: We identified literature by searching Medline and PubMed from January 1995 to December 2011 using the keywords "gastrointestinal stromal tumors", "GIST", "imatinib" and "tyrosine kinase inhibitor". Additional papers were identified by a manual search of the references from the key articles. There were no exclusion criteria for published information to the topics.

Results: For localized primary GISTs, surgical resection is the mainstay of therapy. The 5-year survival rate after complete resection of GISTs is approximately 50%–65%. Many factors including tumor size, mitotic rate, tumor location, kinase mutational status and occurrence of tumor rupture have been extensively studied and proposed to be predictors of survival outcomes. Adjuvant imatinib is proposed as an option for those patients with a substantial risk of relapse. Unresectable metastatic or recurrent GIST can be treated with a tyrosine kinase inhibitor, imatinib, with a remarkable response (50%–70%) and prolonged survival (median progression-free survival: 18–20 months; median overall survival: 51–57 months). The standard approach in the case of tumor progression on 400 mg once per day is to increase the imatinib dose to 400 mg twice per day as permitted by toxicity. Use of a second-line targeted agent, sunitinib, in patients with advanced GIST who fail (or are intolerant of) imatinib therapy is advised.

Conclusion: Treatment for GISTs has become increasingly complex because of the growing understanding of its biology. A multidisciplinary team that includes radiologists, medical oncologists, pathologists, and surgeons is paramount for the effective treatment of GIST.

1. Introduction

Gastrointestinal stromal tumors (GISTs) comprise < 1% of all gastrointestinal (GI) tumors, but GISTs are the most common mesenchymal tumors of the GI tract. In the past, these tumors were classified as leiomyomas, leiomyosarcomas, or leiomyoblastomas. With the advent of immunohistochemistry and electron microscopy, GIST is recognized as a separate entity during the last decade. The overall incidence including incidental small tumors, has been estimated to be 6 to 20 per million.[1–6] GISTs demonstrate a similar distribution between men and women. Although GISTs have been reported in patients of all ages, most patients are between 40 and 80 years old at the time of diagnosis, with a median age of 60–65 years.[1–6] GISTs most commonly occur in the stomach (60%–70%), followed by the small intestine (20%–30%), duodenum (4%–5%), rectum (4%–5%), colon (<2%) and esophagus(<1%).[5–9] On rare occasions, GISTs develop outside the GI tract in the mesentery, omentum, or retroperitoneum.[5–10] 1%–2% of GISTs occur in the pediatric population which are thought to be fundamentally different entities from adult GISTs. They are almost exclusively gastric in origin and, unlike adult GISTs, are more common in girls.

For localized primary GISTs, surgical resection is the mainstay of therapy. It is well known that advanced GIST can be treated with a tyrosine kinase inhibitor imatinib (Gleevec; Novartis Pharma AG, Basel, Switzerland), with a remarkable tumor response and prolonged survival. New second-line targeted agents are now available. Treatment for GISTs has also become increasingly complex because of the growing understanding of biology of this tumor. Therefore, a multidisciplinary team that includes radiologists, medical

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oncologists, pathologists, and surgeons is paramount for the effective treatment of GIST.

This review highlights the overall management of GISTs and its recent developments. Pediatric GIST that requires specialized management is not included in this review.

2. Methods

We identified literature by searching Medline and PubMed from January 1995 to December 2011 using the keywords "gastrointestinal stromal tumors", "GIST", "imatinib" and "tyrosine kinase inhibitor". Additional papers were identified by a manual search of the references from the key articles. There were no exclusion criteria for published information to the topics.

3. Pathology & immunohistochemistry

Primary GISTs are typically well-circumscribed, soft, friable and often highly vascular in nature. GISTs often appear heterogeneous due to necrosis or intratumoral hemorrhage. Large tumors may show ulceration of the overlying mucosa. Microscopically, most GISTs demonstrate 3 main histologic subtypes: spindle cell type (most common), epithelioid type, and mixed spindle and epithelioid type. More than 95% of GISTs are positive for the tyrosine kinase receptor protein KIT, which is detected by the antibody CD117. Other common markers are CD34 (60%–70%) and smooth muscle actin (SMA) (30%–40%). They are typically negative for desmin and S-100 protein (<5% positive). In contrast, leiomyomas and leiomyosarcomas are positive for SMA and desmin, and negative for KIT and CD34, which helps to distinguish GISTs from other mesenchymal tumors.[11–15]

In 1983, Mazur and Clark observed that gastric tumors lacked ultrastructural and immunohistochemical evidence of smooth muscle differentiation and first introduced the term "stromal tumor".[16] In 1998, Kindblom and his colleagues observed that GISTs had immunomorphological similarities to the interstitial cells of Cajal and proposed the term "gastrointestinal pacemaker cell tumor".[17] That same year, Hirota and his colleagues discovered that sequencing of c-kit complementary DNA, which encodes a proto-oncogenic receptor tyrosine kinase (KIT), from five GISTs revealed mutations in the region between the transmembrane and tyrosine kinase domains.[18] All the corresponding mutant KIT proteins were constitutively activated without the KIT ligand. GISTs are believed to arise from the interstitial cells of Cajal, components of the intestinal autonomic nervous system that serve as intestinal pacemakers. These works supported the hypothesis that GIST may indeed develop from stem cells that differentiate toward the interstitial cells of Cajal phenotype and confirmed KIT as an accurate diagnostic tool for GIST.

Immunohistochemical analysis has demonstrated that nearly all GISTs (approximately 85%) contain activating mutations in KIT, which leads to constitutive activation of KIT and its tyrosine kinase function. This receptor, the product of the proto-oncogene c-kit (located on chromosome 4q11q12), can be detected by immunohistochemical staining for CD117. KIT is involved in many cellular functions, including cell differentiation, growth, and survival. Binding of KIT to its ligand leads to dimerization and subsequent autophosphorylation of KIT, which initiates a cascade of intracellular signaling leading to adhesion, differentiation, proliferation, and tumorigenesis. Several mutations have been described. Activating mutations of exon 11 of KIT are the most common mutations. Others include exons 9, 13, and 17. About 5% contain mutations in platelet-derived growth factor receptor-alpha (PDGFRα). KIT and PDGFRα mutations are mutually exclusive. The remainder of GISTs do not contain identifiable mutations in either of these two receptor kinases, otherwise known as "wild-type" GIST (10%–15%).[19–21] Current data suggests that mutational status has both prognostic significance and impact on response to tyrosine kinase inhibitors therapy, which will be discussed in greater detail later in this review.

4. Presentation

The clinical presentation of patients with GIST varies depending on the anatomic location of the tumor, the tumor size and its aggressiveness. GISTs are highly vascular submucosal masses and typically grow outward, away from the originating GI lumen. Small tumors (<2 cm) are most commonly found incidentally during endoscopy, cross-sectional imaging, or laparotomy/laparoscopy for other indications. Most (70%) patients diagnosed with GIST have vague symptoms, such as abdominal pain, GI bleeding from a mucosal erosion, or an abdominal mass.[22,23]

5. Investigation

Initial workup should include a detailed history and a thorough physical examination, followed by cross-sectional imaging to both assess the extent of the primary tumor and evaluate potential sites of metastatic disease, most commonly the liver and peritoneum. Metastases to the lungs or other extra-abdominal locations are usually seen only in very advanced diseases. Lymph node metastases are rare, except in the pediatric population. CT (computed tomography) scan is the imaging modality of choice for initial evaluation, staging, and monitoring of treatment response in GIST. GISTs are visualized as enhancing solid masses and tumor vessels are often noted on contrast enhanced CT scan.[24–26] Small GISTs typically appear as well-defined soft-tissue, relatively low-density masses that appear relatively homogeneous on contrast enhanced CT scan. When the masses are large, they are often heterogeneous because of necrosis, hemorrhage, and myxoid degeneration. Magnetic resonance imaging (MRI) is an alternative option and is indicated for surgical planning in rectal GISTs, for evaluation of liver lesions indeterminate on CT scan, and for cases in which CT scan is contraindicated.[27–30] On MRI, GISTs are generally well defined; the solid portions of the masses are typically of low- to intermediate-signal intensity on T1-weighted images and high signal intensity on T2-weighted images. As in CT scan, the tumors enhance after injection of an intravenous contrast agent. Percutaneous biopsy is not recommended because of the potential risk of peritoneal seeding or tumor rupture, and is indicated only when treatment would be altered.

Contrast-enhanced CT scan plays an important role in surveillance and early detection of tumor recurrence or progression.[24–26] After treatment, tumors become hypodense and their size may gradually decrease and eventually stabilize. Recurrence or disease progression is traditionally diagnosed by finding an increase in tumor size or the development of new lesions at the site of previous disease or by finding distant metastasis. ^{18}Fluoro-deoxyglucose-positron emission tomography (^{18}FDG-PET) is also highly sensitive and specific in detecting GISTs and evaluating their response to treatment.[31–33]

6. Prognostic factors for malignant potential and recurrence

Unlike other GI malignancies, the behavior of GIST is difficult to predict based on histopathology alone. Many factors including tumor size, mitotic rate, tumor location, kinase mutational status and occurrence of tumor rupture have been extensively studied and proposed to be predictors of survival outcomes, but tumor size and mitotic rate are the two most widely accepted indices.[7,34–45]

6.1. National institutes of health (NIH)

In 2001, the National Institutes of Health (NIH) in the USA held a conference of experts with the goal of developing a consensus approach to diagnosis and morphologic prognostication of GIST. One scheme for predicting the risk of recurrence or metastasis of a surgically resected primary GIST was developed by consensus at this meeting and was published by Fletcher et al. in 2002.[39] Tumor size and mitotic index were the foundation for this consensus approach to risk stratification of GISTs. In general, tumors < 5 cm and particularly those < 2 cm have a lower risk of metastasis, whereas tumors > 5 cm and particularly those > 10 cm have a higher risk. Similarly, a mitotic rate of <5 mitoses per 50 high power fields (HPF) portends a low risk of metastasis, whereas mitotic rates > 5 per 50 HPF and particularly those > 10 per 50 HPF predict a higher risk of metastatic disease. These 2 factors are independent but mutually influential predictors and are combined in the NIH guidelines.

6.2. The Armed Forces Institute of Pathology (AFIP)-Miettinen staging system

The US AFIP prognostic criteria developed on the basis of a meticulous assessment of two large series of patients followed up for a median of about 15 years—account for tumor site and provide a more detailed risk stratification. They proposed guidelines that incorporated anatomic location, separating the classical risk factors of tumor size and mitotic count between gastric and small intestinal origin.[7] In general, gastric tumors have a more favorable prognosis than the intestinal tumors with similar parameters. Gastric GISTs $<$ or $=$ 10 cm and $<$ or $=$ 5 mitoses per 50 HPF have a low risk for metastasis, whereas those with >5 per 50 HPF and >5 cm in diameter have a high risk for metastasis. In contrast, all intestinal GISTs >5 cm independent of mitotic rate have at least moderate risk for metastases, and all >5 per 50 HPF have a high risk for metastases. Intestinal GISTs $<$ or $=$ 5 cm with $<$ or $=$ 5 per 50 HPF have a low risk for metastases.

6.3. Memorial Sloan-Kettering cancer center (MSKCC) prognostic nomogram

The MSKCC sarcoma team developed a nomogram to estimate the probability of recurrence-free survival based on tumor size (a continuous variable), location (stomach, small intestine, colon/rectum, or other), and mitotic index (<5 or $>$ or $=$ 5 per 50 HPF) after surgery for 127 patients with primary GIST at MSKCC.[40] The nomogram was tested in patients from the Spanish Group for Research on Sarcomas ($n = 212$) and the Mayo Clinic, Rochester, MN, USA ($n = 148$). Risk scores associated with each factor are first added up; then, the predicted probability of 2-year and 5-year recurrence-free survival can be read from the nomogram. The nomogram was assessed by calculating concordance probabilities and testing calibration of predicted recurrence-free survival with observed recurrence-free survival.

6.4. Mutational status

More recent studies of GIST patients have focused on the effect of mutational status on response to imatinib and other tyrosine kinase inhibitors. The presence and type of KIT mutations have been found to predict response to tyrosine kinase inhibitors in recent studies. Patients with exon 11 mutations have better objective response rate (63%–83.5%) and increased progression free survival than those with exon 9 mutations (34%–47.8%) or wild-type mutations (0%–44.6%).[41–44] However, for those with imatinib resistance or intolerance, GISTs with exon 9 or wild-type mutations have improved responses and progression-free survival to second-line sunitinib than those with exon 11 mutations.[45]

6.5. Treatment for localized operable disease

The treatment strategy of GISTs varies depending on size and tumor location. Complete surgical extirpation remains the cornerstone of GIST management and the only curative treatment. The 5-year overall survival rate after complete resection of GISTs is 50%–65%.[22,46,47] Every effort should be taken to ensure negative resection margins, and wide margins have not been shown to be beneficial. Resection can usually be accomplished with only a wedge resection of the stomach or a segmental resection of the small bowel. Indeed there is no evidence to suggest that more extensive procedures prolong survival or delay recurrence.[48,49] Extensive surgery is occasionally required for large or poorly located tumors, such as those near the gastroesophageal junction, periampullary region, or lower rectum. When GISTs are densely adherent to adjacent organs, en bloc resection should be performed. These tumors should also be carefully handled to avoid tumor rupture, which leads to a very high risk of intra-abdominal dissemination and recurrence.[34,37,38] Because GISTs rarely metastasize to lymph nodes, formal lymphadenectomy is not necessary unless locoregional lymph nodes are enlarged.

6.6. Adjuvant therapy

The outcome of surgery alone have been inadequate, with up to 50% of patients developing tumor local or distant recurrence, with a median time to recurrence of 2 years, and eventually dying from the disease.[22,46,47,50,51] GISTs are notoriously unresponsive to chemotherapy and radiation therapy. With the success of imatinib in the treatment of metastatic GIST, this has prompted investigation into the potential benefit of adjuvant imatinib. Imatinib mesylate is a small molecule that inhibits activation of the KIT and PDGFα proteins by binding to the adenosine triphosphate binding pocket required for receptor phosphorylation and activation. The role of adjuvant imatinib therapy is being actively investigated. The American College of Surgeons Oncology Group (ACOSOG) Intergroup Adjuvant GIST Study Team undertook a randomized phase III, double-blind, placebo-controlled, multicenter trial.[52] Eligible patients had complete gross resection of a GIST at least 3 cm in size and positive for the KIT protein by immunohistochemistry. Patients were randomly assigned to imatinib 400 mg ($n = 359$) or to placebo ($n = 354$) per day for 1 year after surgical resection. At a median follow-up of 19.7 months, 30 (8%) patients in the imatinib group and 70 (20%) in the placebo group had tumor recurrence or had died. Imatinib significantly improved recurrence-free survival compared with placebo (98% vs. 83% at 1 year). Based on these results, in 2008, imatinib was approved at a daily dose of 400 mg by the U.S. Food and Drug Administration (FDA) as adjuvant therapy for high-risk patients following complete surgical resection of GIST. In 2009, the European Medicines Agency approved the use of adjuvant imatinib for the same group of patients. However, controversy over the duration of therapy remains.

6.7. Preoperative therapy - neoadjuvant therapy & tumor downstaing therapy

Preoperative systemic therapy for GIST can be divided into neoadjuvant therapy or preoperative tumor downstaging therapy. Tumor downstaging is a new concept in the management of unresectable malignancy. Strategies that combine the use of imatinib and surgical resection have become the cornerstone of

treatment for these advanced GISTs. The term tumor downstaging should be differentiated from the term neoadjuvant therapy. For neoadjuvant therapy, the tumor is resectable, and the treatment is given preoperatively to improve on the results of surgery. In many patients with large or poorly localized primary tumors that would require extensive surgery or sacrifice of a large amount of normal tissue, neoadjuvant imatinib can lead to reduction in tumor size making surgical resection to be safer and to have a better chance of getting negative margins. For tumor downstaging, the tumor is unresectable before treatment either because of the local extent of the disease or because of distant metastasis.

6.8. Neoadjuvant therapy

As surgery is still the first-line treatment for those operable diseases, the evidence in the medical literature is limited.[53–58] Results of a nonrandomized Phase II trial testing neoadjuvant/adjuvant imatinib for primary advanced and potentially operable metastatic/recurrent GIST, led by the Radiation Therapy Oncology Group (RTOG), were recently published.[54,55] Patients with primary GIST ($\geq$5 cm, group A) or resectable metastatic/recurrent GIST ($\geq$2 cm, group B) received neoadjuvant imatinib (600 mg/day) for approximately 2 months and maintenance postoperative imatinib (600 mg/day) for 2 years. Sixty-three patients were originally entered (53 analyzable: 31 in group A and 22 in group B). Estimated 5-year progression-free survival and overall survival were 57% in group A, 30% in group B; and 77% in group A, 68% in group B, respectively. A median time to progression has not been reached for group A and was 4.4 years for group B. In group A, in 7 of 11 patients, disease progressed >2 years from registration; 6 of 7 patients with progression had stopped imatinib before progression. In group B, disease progressed in 10 of 13 patients >2 years from registration; 6 of 10 patients with progressing disease had stopped imatinib before progression. This long-term analysis suggests a high percentage of patients experienced disease progression after discontinuation of 2-year maintenance imatinib therapy after surgery. Consideration should be given to studying longer treatment durations in intermediate- to high-risk GIST patients.

However, until more confirmatory work is performed, the use of imatinib in the neoadjuvant setting for radiographically resectable disease remains investigational and is not currently recommended. The use of preoperative target therapy should be decided on a case by case basis at centers with experience in the treatment of GIST.

6.9. Preoperative tumor downstaging therapy

There are several prerequisites for a successful neoadjuvant therapy or tumor downstaging and salvage surgery treatment regimen: - 1. An effective treatment which can shrink the tumor in a significant proportion of patients; 2. A close radiological monitor on the tumor response to the treatment; 3. Repeated assessment by surgeon with a view to carry out curative resection at the right time. As the concept of tumor downstaging followed by curative resection is new, the evidence in the medical literature is limited. This was just highlighted by several reported series that illustrate experience with preoperative downstaging therapy with imatinib at various medical centers.[59–61] Following maximal tumour response, generally after 3–6 months, surgery is performed. Despite the limited data, imatinib is the preferred initial treatment for patients with locally advanced unresectable disease. One clear message is that salvage surgery following tumor downstaging gives good survival outcome and the possibility of a cure in a proportion of patients with unresectable GIST. It gives great hope to those patients who in the past had a dismal prognosis. The role of salvage surgery after tumor downstaging in improving disease-free and overall survivals in patients with unresectable GIST should be further investigated in prospective randomized controlled trials.

7. Treatment for locally advanced inoperable disease, metastatic disease and recurrent disease

More than half of the new cases of GIST present with advanced or metastatic disease at diagnosis. Imatinib has revolutionized the management of GIST. A single-patient pilot study confirmed the activity of imatinib in a patient with a rapidly progressive metastatic GIST that was resistant to chemotherapy.[62] This landmark single-patient experience prompted Phase II and III clinical trials to confirm the efficacy of imatinib in the treatment of metastatic or unresectable GIST and rapidly expanded the global development of imatinib.[63–66] Currently, imatinib is used as the first-line treatment for metastatic or unresectable GIST. Imatinib therapy for unresectable or metastatic GIST is typically initiated at a dosage of 400 mg per day. This blockade results in a dramatic tumor response in 50%–70% of patients with advanced GIST, associating with a median progression-free survival and a median overall survival of 18–20 months and 51–57 months.[66–68] The most common non-hematologic toxicities in patients who received imatinib were edema (mainly periorbital), fatigue, nausea, diarrhea, myalgia, skin rash, headache, and abdominal/chest pain. Some of the side effects (e.g., nausea, vomiting, edema, and rash) were reported to decrease during the course of treatment, which may be because of the development of tolerance. The most frequently reported hematologic side effects of imatinib included anemia (dose-related) and granulocytopenia, particularly neutropenia (independent of dose). In 2002, the FDA approved imatinib for treating patients with KIT-positive unresectable and/or metastatic GIST.

Two randomized, phase III studies compared imatinib given at 2 different doses: 400 mg once per day or 400 mg twice per day in Europe and Australasia, and North America. The European Organization for Research and Treatment of Cancer (EORTC) and Australasian Gastro-Intestinal Trials Group (AGITG) performed the study in which 946 patients with advanced GIST were randomized to 400 mg of imatinib once or twice per day.[67] At a median follow-up of 760 days, 263 of 473 patients (56%) allocated to imatinib once per day had progressed compared with 235 of 473 (50%) who were assigned to treatment of twice per day. Treatment responses were noted equally with both regimens. Overall survival estimates were 85% at 1 year and 69% at 2 years in patients treated once per day, and 86% at 1 year and 74% at 2 years in those treated twice per day. Imatinib was fairly well tolerated in both arms. More dose reductions and treatment interruptions were observed with higher-dose imatinib. The Southwest Oncology Group Intergroup trial randomized 746 patients with advanced GIST to imatinib 400 mg once per day or 400 mg twice per day.[68] The trial reported nearly identical response rates (40% vs. 42%). With a median follow-up of 4.5 years, a median progression-free survival was 18 months for patients on the standard-dose arm, and 20 months for those receiving high-dose imatinib. Median overall survivals were 55 and 51 months, respectively. There were no statistically significant differences in objective response rates, progression-free survival, or overall survival. After progression on standard-dose imatinib, 33% of patients who crossed over to the high-dose imatinib regimen achieved either an objective response or stable disease. There were more severe toxicities noted on the high-dose imatinib arm. Both studies showed equivalent response rates and overall survival at both dose levels. A higher dose of imatinib was associated with more side effects than a lower dose in both studies. Both the studies confirmed the starting dose of 400 mg per day for most patients. The results of the meta-analysis of 1640 patients from both trials showed a small progression-free survival advantage of high-dose

imatinib, essentially among patients with KIT exon 9 mutations, but no overall survival advantage.[69] Based on the current evidence, two groups benefited from the treatment with 400 mg twice daily of imatinib: (1) patients with disease progression on standard-dose therapy, and (2) patients whose tumor harbors an exon 9 mutation in KIT.

The duration of imatinib therapy in advanced GIST has been evaluated in two French Sarcoma Group phase III randomized studies separately evaluating outcomes of patients with responding or stable disease to interruption of treatment after 1 year and after 3 years of imatinib, respectively.[70,71] The first study, 58 patients with response or stable disease under imatinib who reached more than 1 year of follow-up were randomized between May 2003 and April 2004 to 32 and 26 patients in the interruption and continuation arms, respectively.[70] In October 2005, eight of 26 patients in the continuation group and 26 of 32 patients in the interruption group had documented disease progression. Twenty-four of 26 patients with documented progression in the interruption arm responded to imatinib reintroduction. No differences in overall survival or imatinib resistance were observed between the two arms. In another study, 50 patients with non-progressive disease who had received 3 years of treatment with imatinib were randomly assigned between June, 2005, and May, 2007 to the interruption and continuation arms, 25 patients in each group.[71] After a median follow-up of 35 months, 2-year progression-free survival was 80% in the continuation group and 16% in the interruption group. For these reasons, imatinib treatment is usually continued indefinitely in the absence of disease progression or unacceptable toxicity, since treatment interruption is generally followed by relatively rapid tumor progression in virtually all patients.

Progression on first-line therapy with imatinib on GIST is caused by either initial resistance or more often a secondary mutation in tyrosine kinases KIT or PDGFR. The standard approach in the case of tumor progression on 400 mg once per day is to increase the imatinib dose to 400 mg twice per day as permitted by toxicity. Around one-third of patients with unresectable and/or metastatic GIST, who fail on 400 mg per day of imatinib, show response or have stable disease with the escalated doses.[72] Those who have progressive diseases, or are intolerant of imatinib, are treated with a second-line tyrosine kinase inhibitor, sunitinib malate (Pfizer, New York, NY) at a dose of 50 mg per day in a 4-weeks-on/2-weeks-off regimen. Sunitinib is a small molecule, oral, multi-targeted tyrosine kinase inhibitor with potent anti-angiogenic and anti-tumor activities, targets receptors of KIT, vascular endothelial growth factor receptor (VEGF1, 2, 3), platelet-derived growth factor (PDGFA and B), Fms-like tyrosine kinase-3 (FLT3), and a receptor encoded by ret proto-oncogene (RET). Demetri and colleagues published their double-blind randomized, phase III trial comparing sunitinib in 207 patients and placebo in 105 patients who had advanced GIST resistant to or intolerant of previous treatment with imatinib.[73] The median time to tumor progression was 27.3 weeks in patients receiving sunitinib and 6.4 weeks in those on placebo. The therapy was reasonably well tolerated, and the most common treatment-related adverse events were fatigue, diarrhea, and skin discoloration. In 2006, the FDA approved second-line use of sunitinib in patients with advanced GIST who fail (or are intolerant of) imatinib therapy. In another study, progression-free survival was significantly longer for patients with primary KIT exon 9 mutations (19.4 vs. 5.1 months) or with a wild-type genotype (19 vs. 5.1 months) than for those with KIT exon 11 mutations.[45] Alternatively, a regimen consisting of a daily dose of 37.5 mg may be used. A phase II study evaluated whether continuous daily dosing at a lower dose of 37.5 mg per day would be potentially as efficacious and less toxic than the 4/2 schedule.[74] The overall clinical benefit rate was 53% (13% experienced partial responses and 40% stable disease). The median progression-free survival was 34 weeks and the median overall survival at the time of analysis was 107 weeks. No new adverse events were apparent compared with the approved intermittent dosing schedule. The results of this study suggest that continuous daily dosing appears to be an effective alternative dosing strategy with acceptable safety for patients.

8. Conclusion

The last decade marked an important era in the history of GIST, culminating from the advancement of diagnosis of GIST and our understanding of its pathogenesis, to the development of risk prognostic score and consequently, influencing treatment strategies. This translation of laboratory successes into biologically relevant therapeutics dramatically improves patient outcomes. Future studies should focus on how to integrate the molecular therapy well with surgery for the management of operable or inoperable GIST. Large multi-institutional clinical trials to investigate the efficacy of imatinib as adjuvant or neoadjuvant therapy for GISTs are now required.

Conflict of interest

LWY proposed the idea, structure, and content of this article. LWY also did the revision and final proof read of the article. LECH proposed the idea, did the literature search and wrote the first draft. LSHY did the literature search and proof read of the article.

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