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Treatment Options for Gastrointestinal Stromal Tumors

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1. Introduction

The term gastrointestinal stromal tumor (GIST) in the description of a specific group of gastrointestinal nonepithelial tumors lacking the microscopic evidence of smooth muscle or characteristics of neural immunoreactivity was first introduced by Mazur and Clark (Mazur & Clark, 1983). The common origin of GIST and interstitial cell of Cajal (ICC), the pacemaker cells in the digestive tract, was proposed due to their immunohistochemical and ultrastructural similarities. The definition of GISTs as tumors originating from ICC was further confirmed according to the findings that both GIST and ICC express KIT and that most GISTs have gain-of-function mutations of *KIT*, the proto-oncogene that encodes a 145 kDa transmembrane tyrosine kinase KIT receptor. Mutation of different exons of the *KIT* oncogene results in activation of the tyrosine kinase activity of KIT, leading to ligand-independent kinase activity and uncontrolled cell proliferation as well as resistance to apoptosis (Demetri et al., 2002; Hirota et al., 1998; Kindblom et al., 1998; Savage & Antman, 2002). More than 90% of GIST have constitutive activation of the KIT protein as a result of *KIT* mutation and in GIST without KIT mutations, gain-of-function of platelet derived growth factor receptor α (PDGFRA) are present in about one-third of cases. It was recently proposed that ETV1, one of the ETS family transcription factor, can be a lineage survival factor that cooperates with KIT in gastrointestinal stromal tumours. GIST arises from ICCs with high levels of endogenous ETV1 expression that, when coupled with an activating KIT mutation, drives an oncogenic ETS transcriptional program (Chi et al., 2010; Roberts & Eisenberg, 2002; Rubin et al., 2001).

GIST was estimated to occur in about 14.5 cases per million and was the most common mesenchymal tumor of the gastrointestinal tract. The most common locations of GIST are the stomach (50-60%), small intestine (20-30%), colon and rectum (10%), and esophagus (5%). Patients mostly present with nonspecific symptoms and signs (69%) and initial metastasis was noted in about 15-50% of GISTs (DeMatteo et al., 2000; Fletcher et al., 2002; Nilsson et al., 2005; Roberts & Eisenberg, 2002; Shinomura et al., 2005).

The accurate diagnosis of GIST should be based on tumor morphology and immunohistochemistry. GIST tumors grossly appear as well-defined submucosal lesion with prominent vasculature and occasional hemorrhage or ulceration (Fig. 1A and 1B.). Under morphologic examination in the immunohistochemical analysis, GIST tumor cells are

generally classified as three morphologic subtypes, including spindle cell type in the majority, epithelioid cell type and mixed type composed of both spindle and epithelioid cells (Fig. 1C). Similarly, tumor cells in GIST cell lines *in vivo* presents as spindle cell morphology in the majority, regardless of the types of the GIST cell line (Fig. 1D).

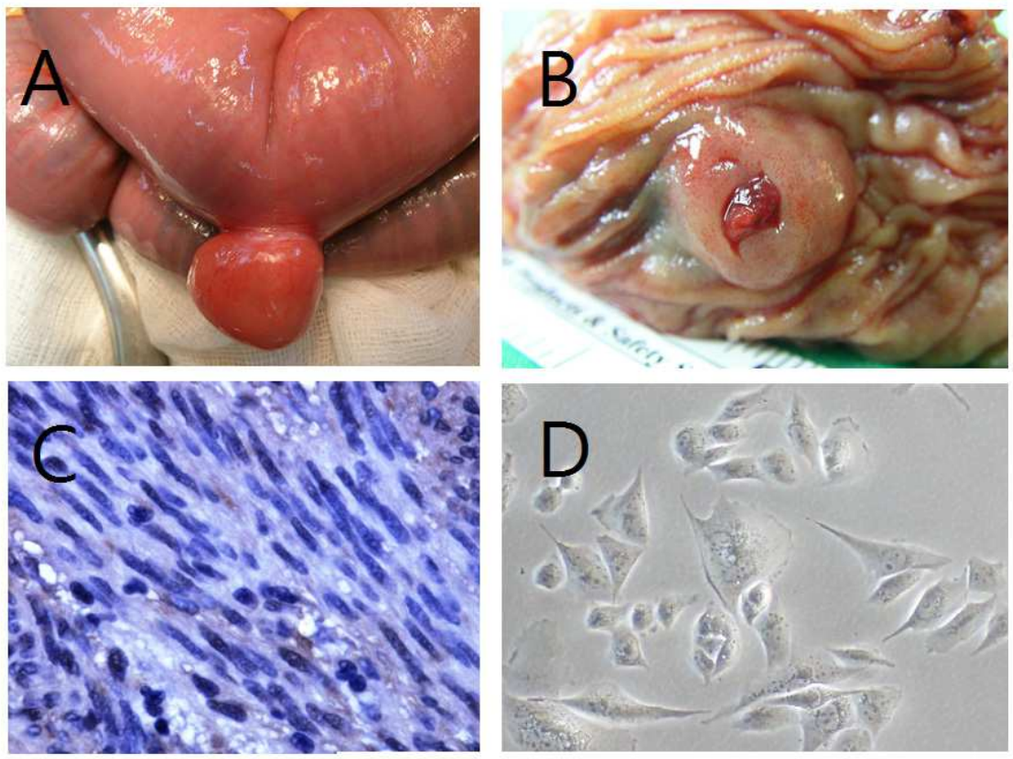

Fig. 1. Macroscopic and microscopic inspection of GIST tumor.
A. Small intestinal GIST. B. GIST tumor with central ulceration. C. GIST tumor cell by immunohistochemical staining demonstrating both types of spindle and epithelioid tumor cells. D. GIST tumor cell line.

In the diagnosis of GIST, KIT has been shown to be a specific and sensitive marker in the differential diagnosis of gastrointestinal mesenchymal tumors. The majority of GISTs express KIT, and approximately only 4-5% of GISTs are KIT negative. There may be different KIT-staining patterns KIT-negative GISTs preferentially occur in the stomach and usually show pure epithelioid or mixed cytomorphology (Debiec-Rychter M ei al., 2004; Hirota et al., 1998; Kindblom et al., 1998; Medeiros et al., 2004).
In recent years, numerous antibodies for the diagnosis of GIST have been identified. These immunohistochemical markers were mainly noted and verified in molecular studies and may be of value in the diagnosis in KIT-negative GISTs. Discovered on GIST (DOG1), an up-regulated transmembrane protein found in GISTs, is one of the markers of significance. Recent studies have demonstrated that antibodies against DOG1 have greater sensitivity and specificity than KIT (CD117) and CD34, serving as specific immunohistochemical markers for GIST regardless of the KIT/PDGFRA mutation or KIT immunohistochemical expression. Carbonic anhydrase II (CA II) and protein kinase C (PKC)-theta, a member of

the protein kinase C family, in addition to being biomarkers frequently expressed in the majority of GISTs with high specificity, are also of diagnostic as well as prognostic values (Blay et al., 2004; Duensing et al., 2004; Espinosa et al., 2008; Lee et al., 2008; Liegl et al., 2009; Miettinen et al., 2009; Parkkila et al., 2010; West, RB et al., 2004).

The role of biopsy in the diagnosis of GIST is unclear. In tumors with fragile consistency and hypervascularity, biopsy is not suggested due to risk of bleeding, capsular perforation with rupture and tumor seeding. Although tissue biopsy can be conducted safely and accurately by endoscopy or other image-guided methods, the submucosal location of the tumors often make accurate sampling difficult. Necrosis, ulceration and hemorrhage are common in GIST tumor tissues and may limit and preclude the feasibility and plausibility of fine needle aspirates or core biopsies. In certain situations, biopsies may be of value in differential diagnosis when other disease entities are suspected or when diagnosis is necessary for subsequent planning of treatment (Garcia dePolavieja et al., 2010)

Imaging studies play a diagnostic role for evaluation of suspected GIST patients for characterization of the tumor. Contrast-enhanced computerized tomography (CT) scanning and occasionally magnetic resonance imaging (MRI) are the imaging modality of choice for initial evaluation and [^{18}F]2-fluoro-2-deoxy-D-glucose-positron emission tomography (FDG-PET)/CT has recently become important in both diagnosis and assessment of tumor response to targeted therapy in the adjuvant as well as neoadjuvant therapy in GIST.

For small tumors found incidentally, CT scanning or endoscopic ultrasound is recommended (Blackstein et al., 2006; Van den Abbeele et al., 2008).

While the treatment of GISTs with radiotherapy or systemic chemotherapy was unsuccessful in the majority, complete surgical resection remains the gold standard in the management of primary GIST. The recurrence rate of GIST, even in patients with resectable GIST, ranges from 17 to 24% in some series but chas also been reported to be as high as 80%. The median survival for patients with recurrence is about 9-12 months (Demetri et al., 2002; Iesalnieks et al., 2005; Nilsson et al., 2005 ; Shinomura et al., 2005; Zhu et al., 2010).

Imatinib mesylate, an tyrosine kinase inhibitor (TKI) for both normal and mutated KIT found in most GISTs, was the first effective drug in the treatment of metastatic GIST and was approved by the Food and Drug Administration (FDA) for the treatment of unresectable and metastatic GIST in 2002 (Kwon et al., 2001; DeMatteo et al., 2002; Demetri et al., 2002; Savage & Antman, 2002). Adjuvant therapy with imatinib theoretically might improve the curative rate after complete resection of primary GIST by eradicating residual microscopic disease. Trials on adjuvant imatinib after complete resection of primary GIST have been evaluated in patients with a substantial risk of relapse. Recent studies confirmed that adjuvant target therapy with imatinib was effective in improving disease-free survival in GIST after surgery in high-risk patients , potentiating upcoming wide clinical application of adjuvant imatinib treatment in GIST. Since the introduction of imatinib as the target therapy for treatment of advanced GIST, acquired or secondary resistance to imatinib was found to develop in some GIST patients (Corless et al., 2004; Dematteo et al., 2009; Demetri et al., 2002; Heinrich & Corless, 2005; Verweij et al., 2004). Another tyrosine kinase inhibitor, sunitinib malate has recently been approved as a second-line treatment for GIST patients who develop resistance to or cannot tolerate imatinib. Sunitinib has also been approved by the US FDA as second-line therapy for patients with advanced GIST. Newer agents are currently being evaluated in clinical trials. Identifying factors or biomarkers predicting high

risk of disease progression in GIST patients thus becomes increasingly important and has been reported in numerous studies (Blanke et al., 2009; Corless et al., 2004; Keun et al., 2008). Numerous studies have been devoted to the identification of specific clinical and pathological markers of prognostic significance (Hsu et al., 2007a, 2007b, 2010a, 2010b; Kwon et al., 2001; Miettinen et al., 2002; Rudolph et al., 1998 ; Yan et al., 2003). Among miscellaneous prognostic parameters, tumor size and mitotic figure have been considered most useful and reliable predictive variables for prognosis with good reproducibility and statistical consistency. A Consensus guidelines and classification system for GIST risk stratification, referred to as the National Institutes of Health (NIH) Consensus Criteria for GIST risk stratification, that categorizes GIST patients with GIST into low, intermediate, and high-risk groups according to these two parameters has been proposed and was widely applied in the clinical setting for risk analysis for patients with GIST (Hsu et al., 2007a, 2007b; Fletcher et al., Shinomura et al., 2005).

Recently, the integration of tumor locationas the third parameter in NIH Consensus Criteria for GIST risk stratification, with intestinal localization of the tumor being a poor prognostic factor, was proposed to help more accurately predicting risk of recurrence and poor prognosis after surgery in patients with GIST, so that potential candidates for adjuvant imatinib therapy can be identified (Gold et al., 2009; Joensuu, 2008; Patel, 2011).

With the advent and rapid progress in the development as well as application of TKI in GIST, the treatment of GIST evolves significantly in recent years. Adjuvant, neoadjuvant therapy and new TKI agents are among the most focused issues of intensive investigations in the management of GIST in the post-TKI era. Revolutionary innovations in surgical techniques such as newly developed laparoscopic modalities have also contributed to the armamentarium of GIST management. Treatment options for GIST with respect to disease stages and different intervention strategies will be presented in this chapter.

2. Primary resectable GIST

2.1 General principles of surgery

Surgical resection has been the standard treatment for patients with localized, resectable GISTs. Specific surgical strategies are required according to the organ involved, tumor location, and tumor size. The goal of resection is to achieve complete (R0) excision of the tumor with negative margins, in the absence of residual disease grossly and microscopically. In general, primary GIST tumors tend not to invade surrounding organs or tissues. Wedge or segmental resection of the involved organs or tissues bearing the tumor is adequate. Lymph node metastasis is uncommon and lymphadenectomy has been considered unnecessary in GIST. In rare occasions when enlarged nodes are found at the time of operation, these should be removed with the primary GIST tumor. It is generally acceptable that a margin of 2 cm be adequate. However, there are no prospectively collected data available with regard to the adequate margin and to whether the extent of resection margins correlate with the risk of tumor recurrence or metastasis.

During operation, care should be taken to thoroughly evaluate the peritoneal cavity, especially the liver and peritoneum, the most common sites of disease spread for metastasis. Suspicious peritoneal lesions should be resected. Extreme care should also be taken during manipulation of the tumor to prevent excessive bleeding and peritoneal dissemination of tumor cells so that tumor rupture, one of the contributing factors associated with recurrence, does not happen.

Before the TKI era, surgery was the only curative and effective treatment for GISTs. Recemt studies have proved that adjuvant imatinib can delay recurrence and improve survival in selected patients with high-risk GIST. In patients with advanced or metastatic GIST, imatinib is the standard treatment, wiht surgery of residual masses being an option. Preoperative imatinib is an emerging and promising treatment of choice for patients with initially unresectable GIST. Such neoadjuvant therapy offers the chance of converting or reduction of the unresectable GIST into resectable diseases.

2.2 Surgery in relation to tumor location

2.2.1 Gastric GIST

The stomach is the most common tumor location for GISTs. Patients often present with GI bleeding or obstruction. Their diagnosis and are usually made by endoscopy and endoscopic ultrasound that identifies the intramural origin of the tumor. Biopsy occasionally may of help in the diagnosis of GIST. Small tumors are occasionally found during endoscopy for other indications and endoscopic resection when feasible may be indicated. Surgical intervention is necessary for gastric GIST not amenable to endoscopic resection and depends primarily on the location and size of the tumor within the stomach. As with all GISTs, the principle operative treatment is complete resection with negative margins. Special care should be taken to prevent potential tumor rupture by meticulously manipulating the tumor during the operation. The location of GIST in the lower third of the stomach may be a favorable factor, however, the exact significance of different tumor sites for prognosis of gastric GISTs needs to be further clarified. Most would advocate a distal gastrectomy with Billroth I or II reconstruction in tumor of considerable sizes. Proximal lesions on the lesser curve orlocalization close to the gastroesophageal junction may be difficult to surgical resection, especially in tumors with large-sized or wide base. In tumors that become adherent to adjacent structures, en bloc excision with omentectomy, splenectomy, or distal pancreatectomy may be indicated to ensure capsule integrity as well as R0 resection. Unlike gastric cancer, omentectomy or lymphadenectomy is not necessary unless the presence of involvement by intraoperative evaluation (Gervaz et al., 2009; Huang et al., 2010; Miettinen et al., 2005; Privette et al., 2008; Silberhumer et al., 2009).

2.2.2 Small intestinal GIST

The incidence of GIST originating from the small intestine is secondary to that of gastric GIST. Small intestinal GIST of duodenal origin is rare with the incidence of less than 5%. While a majority of patients present with bleeding, large tumors can lead to GI obstruction. The best modality for diagnosis of duodenal GIST is endoscopy. Similar to gastric GIST, the operation depends on the size and location of the primary tumor as well as distance from the ampulla. One recent study showed that type of operation was not correlated to operative risk and disease recurrence, limited operation rather than more radical pancreaticoduodenectomy should be attempted whenever possible for duodenal GIST without involvement of papilla of Vater to preserve more pancreas parenchyma, duodenum, and common bile duct (Chung et al., 2010; Miettinen et al., 2003; Yang et al., 2009).

Intestinal GIST other than duodenal origin can be difficult to diagnose. CT or capsule endoscopy are optional tools in diagnosis. In this disease entity, there is a higher proportion of lesions found in the jejunum than the ileum. The same surgical principles of negative

margins and prevention of tumor rupture apply equally to intestinal GISTs, regardless of the tumor location. This is best accomplished by segmental small bowel resection with primary anastomosis. As mentioned earlier, intestinal location was an independent predictor of recurrence and poor prognosis (Dematteo et al., 2008; Miettinen et al., 2005, 2006).

2.2.3 Colorectal GIST

Reports regarding GIST of colon and rectal origin have been limited in number due to its rarity. Surgical consideration of these colorectal GISTs is the same as that mention in GIST of other locations and may include local exicision or radical resection. However, for rectal GISTs, its rarity makes it difficult to assess the role of the extension of the surgical resection of the tumor. Colonic GISTs are typically treated with segmental resection and primary anastomosis. Unlike colon cancer, formal lymphadenectomy is not necessary unless obvious nodal involvement is present. Resection of rectal GISTs is more difficult and is often associated with increased rate of complication. A formal mesorectal excision is unnecessary and often leads to increased morbidity. One study retrospectively analyzed clinical characteristics of surgically treated gastrointestinal stromal tumors of the colon and rectum and demonstrates that the majority of colorectal GISTs are high-risk. Patients with high-risk colorectal GISTs have a significant likelihood of developing metastases that is associated with poor prognosis. These patients need to be closely followed for an extended period and should be considered for adjuvant therapy with tyrosine kinase inhibitors. Since rectal GISTs are often advanced, the role of neoadjuvant Imatinib in rectal GIST has also been evaluated. It has been proposed that preoperative Imatinib therapy can contribute to reduction of the size in large rectal GISTs, improving the chances of successful radical surgery and therefore decreasing the risk of morbidity and mortality (Hassan et al., 2006; Hou et al., 2009; Machlenkin et al., 2010; Mandalà et al., 2007).

2.3 Endoscopic resection

Small GIST lesions are often found incidentally during endoscopy or laparotomy for specific indications. The diagnosis of GIST is often made after endoscopic ultrasound (EUS) referral for the evaluation of submucosal lesions. Its diagnostic yield can vary. It can be as low as 68.7% without tissue acquisition and as high as 84% with tissue acquisition (Scarpa et al., 2008). When GISTs are accidentally found during routine endoscopy, decision-making may be difficult because of the lack of data regarding biology behavior, invasiveness and metastatic potential of these tumors. Endoscopic features are unable to predict tumor behavior reliably. Once a diagnosis of GIST is confirmed and metastatic disease excluded, subsequent surgical intervention should take into consideration the size and location of the tumor. Treatment of small lesions incidentally found during endoscopy, imaging studies, or surgical exploration for other indications remains controversial. It is agreed that small tumors identified at the time of laparotomy or laparoscopy be removed whenever possible without increasing the risk of tumor rupture or risk of complication such as perforation or hemorrhage. A reasonable strategy can include close follow-up and surveillance in 6–12 months. For lesions more than 2 cm in size, surgical resection is the principle treatment and is the only curative treatment of choice. Endoscopic ligation and resection shows promise as a safe and feasible technique to treat small EUS-suspected gastric GISTs (Casali et al., 2010).

2.4 Minimally invasive surgery

The role of laparoscopic approaches in the surgical management of GIST has gained increasing popularity due to the technical advantage of complete resections in a minimally invasive manner. With appropriate handling of the tumor, laparoscopic surgery has been proved safe and effective in selected patients. Laparoscopy is particularly being used with increasing frequency for GIST originating from the stomach. Laparoscopic resection of gastric GISTs appears technically feasible and is associated with favorable outcomes. It is generally agreed that tumors up to 5 cm can be safely approached laparoscopically. It is also important to follow the same surgical principles of laparotomy when performing laparoscopic GIST resections, including complete R0 resection with free margins, avoidance of accidental tumor rupture intraoperatively, and use of a retrieval bag to prevent spillage and seeding of tumor cells into the peritoneum. While there has been no prospective randomized trial directly comparing laparoscopic and open approaches for gastric GIST, several retrospective series have demonstrated that the laparoscopic approach is associated with low morbidity, mortality, and satisfactory oncologic results. Laparoscopic surgery can be conducted in combination with intra-operative endoscopic assistances according to tumor size and location. Innovative techniques in laparoscopic surgery, including single-port laparoscopic surgery or incisionless surgical approach such as natural orifice transluminal endoscopic surgery (NOTES), have been applied in clinical practice in recent years. These surgical approaches have been reported to be associated with significantly fewer complications, reduced pain, faster recovery, and improved cosmesis compared with traditional open or laparoscopic approaches. It is likely that these newly developed minimally invasive surgery will be applied to miscellaneous surgical diseases, including GIST, in the near future (Catena et al., 2008; Choi et al., 2007; Horgan et al., 2011; Karakousis et al., 2011; Kingham & DeMatteo, 2009; Novitsky et al., 2006; Otani et al., 2006; Privette et al., 2008; Sasaki et al., 2010; Sexton et al., 2008Woodall et al., 2009).

2.5 Adjuvant therapy

The success of IM in the treatment of metastatic GIST and the significant risk of recurrence of GIST in the pre-TKI era with surgery alone stimulated investigation of complete surgical resection in combination with TKI treatment as adjuvant intent. The efficacy of standard dose adjuvant imatinib mesylate (400 mg/day) has been evaluated in clinical trials. The American College of Surgeons Oncology Group (ACOSOG) sponsored two randomized, double-blind, placebo-controlled studies evaluating adjuvant imatinib in completely resected, localized primary GIST. Based on the positive results from these clinical trials, the US FDA approved 400 mg/day imatinib mesylate tablets for oral use for the adjuvant treatment of adult patients following complete gross resection of gastrointestinal stromal tumor (GIST) with tumors larger than 3 cm on December 19, 2008 (DeMatteo et al., 2009). Several studies reported similar outcomes demonstrating that imatinib used in the adjuvant therapy improved recurrence-free survival significantly (Essat & Cooper, 2011). The duration of adjuvant therapy remains controversial and was not specified in the Food and Drug Administration approval since the rate of recurrences in the imatinib mesylate treated group seemed to increase at 18 months from surgery which corresponded to 6 months after discontinuing the study drug. Similar times to progression were also noted after treatment interruptions in patients with metastatic disease.New trials for evaluation of optimal duration for adjuvant therapy are currently undergoing that includes two large European

trials aimed to clarify and evaluate the adjuvant duration: the Scandinavian Sarcoma Group (SSG) and the German Arbeitgemeinschaft Internistische Onkologie (AIO) are jointly conducting a randomized, phase III trial (SSGXVIII/AIO) to evaluate 1 year versus 3 years of adjuvant imatinib mesylate, inhigh-risk GIST patients. The European Organization for Research and Treatment of Cancer (EORTC) 62024 study compares adjuvant therapy for 2 years with observation (Blay et al., 2007).

3. Recurrent GIST

Surgery is the mainstay of treatment for primary resectable GISTs when there is no evidence of metastases or advanced diseases. Although surgery is the only known potentially curative treatment for primary resectable or marginally resectable GISTs, 40–90% of surgically treated patients experience disease recurrence despite complete surgical resection according to the literature. Five-year recurrence-free and disease-free survival rates of 49% and 65%, respectively, have been reported for patients undergoing complete resection. Prevention or identification of risk factors associated with increased rate of recurrence thus become one important issue in the surgical treatment of GIST (Hassan et al., 2008; Rossi et al., 2003; Singer et al., 2002).

Although it is clear that rupture of GIST tumor at operation carries a high risk of tumor recurrence, appropriate surgical management options and the associated outcomes in patients with a ruptured GIST is not clarified. One recent report showed that the risk of recurrence approaches nearly 100% in patients with GIST that ruptured into the abdominal cavity before or during operation and the associated recurrence-free survival was less than 1 year, emphasizing the necessity of adjuvant therapy in these group of high-risk patient. Another study investigates long-term follow-up of the imatinib mesylate treatment in patients with GIST would experience tumor recurrence or metastasis after radical resection and found that the imatinib mesylate treatment could prolong the survival of the patients who have recurrent GIST after the radical surgery (Zhu et al., 2010).

4. Advanced/metastatic GIST and targeted therapy

Initial metastasis can be present in about 15-50% of GIST patients (DeMatteo et al., 2000; Roberts & Eisenberg., 2002; Shinomura et al., 2005). Treatment guidelines for GIST all recognize imatinib as the standard of care for patients with advanced, unresectable, and metastatic GISTs. Imatinib mesylate has been proven to play a significant role in the treatment of advanced/metastatic GIST and has been considered the standard first line therapy in this patient group. Prognosis of patients with advanced disease improved significantly following the approval of imatinib mesylate in 2001 by FDA for this indication. The overall survival can be improved significantly in patients with advanced GIST. Patients who develop resistance to or are intolerant of first-line imatinib mesylate are commonly treated with sunitinib malate, a multi-targeted tyrosine kinase inhibitor approved by the FDA in January 2006 as second-line therapy in this disease (Blanke et al., 2008; Casali et al., 2009; Demetri et al., 2000, 2002, 2006; Nishida et al., 2008).

In the majority of patients with advanced, unresectable or metastatic GIST receiving imatinib treatment shows variable response. Response to treatment can be evaluated on CT scan as reduction of the tumor size or as decreased FDG uptake on a PET/CT scan. In the minority of cases, tumor progression develops within the first 6 months in spite of

treatment, refered to as primary resistance, and in a subset of patients, the tumor may remain unchanged despite treatment. Secondary resistance is defined as situations when patients with initially good response or stable disease develop tumor progression after 12-36 months of treatment. Molecular mechanisms responsible for primary resistance differ from those of secondary resistance. *KIT* exon 9 and *PDGFRA* mutations more commonly are associated with primary imatinib resistance when compared to *KIT* exon 11 mutations. Secondary resistance is most commonly related to secondary mutations in the KIT kinase domain (Gajiwala et al., 2009; Heinrich et al., 2006, 2008; Liegl et al., 2008).

The success and significant effects of imatinib mesylate and sunitinib malate in their clinical application have led to miscellaneous investigations on a wide variety of new TKI for their potential roles in the treatment of GIST, including Nilotinib, Sorafenib, Masitinib (AB1010), Vatalanib (PTK787/ZK 222584). The majority of these multi-targeted tyrosine kinase inhibitors are designed as novel or third-line agents for treatment in imatinib-resistant GIST or imatinib and sunitinib-resistant GIST. If proved of their efficacy against GIST in currently clinical trials, these novel TKI agents will bring about a new TKI era and will definitely hold promise for future targeted therapy in GISTs (Guo et al., 2007; Joensuu et al., 2011; Le Cesne et al., 2010; Prenen et al., 2006; Sawaki et al., 2011).

5. Neoadjuvant therapy

Neoadjuvant, or downsizing treatment, defined as surgical resection for patients with previously unresectable GISTs after treatment with imatinib or other TKI, is indicated for reduction of tumor volume and for eradicating potential microscopically metastatic tumor cells prior to surgery. The rationale for neoadjuvant imatinib is based on the elimination of microscopic and metastatic disease, with additional benefits of preoperative cytoreduction of tumors, facilitating complete resection and function-sparing surgical procedures, offering selected patients with initially unresectable diseases chances of resectability and operability. In addition, if a significant response of tumor to such neoadjuvant therapy can be achieved, the risk of tumor rupture during surgical manipulation, and thus the potential of post-operative recurrence, can also be reduced theoretically.

Neoadjuvant therapy should be individualized and is indicated for patients with large tumors where resection would cause undo morbidity or functional deficit, and small tumors in difficult to treat areas such as the gastroesophageal junction or low rectum. Retrospective reports and prospective investigations evaluating the efficacy of imatinib in the neoadjuvant therapy for GIST have demonstrated promising results in terms of cytoreduction and facilitating conservative, organ-preserving surgery, as well as survival and prognostic benefits (Abhyankar & Nair, 2008; Andtbacka et al.,2007; Blesius et al., 2011; DeMatteo et al., 2007; Eisenberg et al., 2009; Fiore et al., 2009; Sjölund et al., 2010).

As a general, neoadjuvant imatinib should be considered if surgery could result in significant morbidity or loss of organ function, and subsequent surgery may be considered 4 to 12 months later after maximal tumor size reduction. Similar to adjuvant therapy, it remains relatively controversial as to the optimal duration of neoadjuvant therapy as well as the optimal timing of surgical intervention in this particular group of GIST patients. It is proposed that he timing of the surgical procedure can be critical in that resection should be conducted upon maximal response of the tumor to neoadjuvant imatinib before the development of tumor progression. The majority of patients with advanced GIST reach a response within 6 months of neoadjuvant therapy, with a median time to response of 3

months. In patients with GIST responding to neoadjuvant therapy, the time interval before potential resection should not be less than 3 months. Patients can be followed closely with serial CT scans to assess and document progressive reduction of the tumor size (Gold & DeMatteo, 2006, 2007).

PET scan is of importance in the neoadjuvant therapy for GIST in its role as an early and sensitive imaging tool for evaluation of the response of GIST to neoadjuvant treatment in the clinically setting. PET scans can help document tumor activity if the biologic effect of imitinab is unclear clinically. Response of the tumor can be detected and determined by PET after a week or less of neoadjuvant treatment and precedes CT response by several weeks. This could be of great value in patients with unresectable and advanced GIST, for which timely and accurate assessment of tumor response to adjuvant treatment is imperative to subsequent surgical strategies (Bumming et al.,2003; Dimitrakopoulou-Strauss et al., 2007; Katz et al., 2004; Lo et al., 2005; Loughrey et al., 2005; Raut & DeMatteo, 2008; Rutkowski et al., 2006; Shah et al., 2005; Stroobants et al., 2003; Yoon & Tanabe, 2007).

It may be a matter of time when neoadjuvant therapy, like adjuvant therapy, becomes standard treatment of choice in selected GIST patients with advanced or initially unresectable diseases if the optimal duration of treatment in both adjuvant and neoadjuvant therapy can be documented and substantiated.

6. Conclusion

The management of human malignancies, including GIST, requires a multidisciplinary team approach. In primary resectable GIST, the standard treatment remains surgery, which takes into consideration tumor location and tumor size in preoperative assessment. Innovation and evolvement in surgical techniques in the treatment of GIST should always accompany the general surgical principle of complete resection with negative margin and meticulous manipulation of tumor without rupture. The success of targeted therapy with imatinib mesylate in the treatment of advanced/metastatic GIST has revolutionized the management of GIST: in addition to emerging clinical investigations evaluating the effects of novel tyrosine kinase inhibitors in GIST, the significant role of imatinib mesylate and other tyrosine kinase inhibitors in the adjuvant and neoadjuvant therapy in different GIST patient groups has been proved and substantiated. The importance of adjuvant as well as neoadjuvant therapy in the management of GIST will continue to be emphasized and verified. It is likely that future treatment in GIST will move toward individualized targeted therapy in combination with surgery in order to optimize clinical outcomes including improved survival, reduced risk of recurrence and better quality of life.

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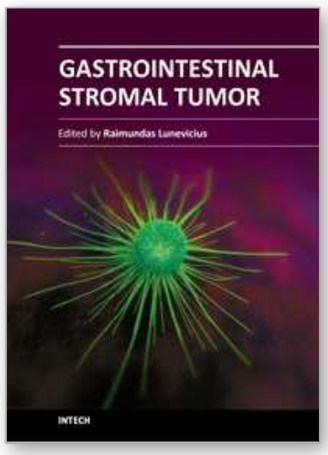

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Almost 30 years have gone by since the postulation that GISTs derive from mesenchymal stem elements, and only 15 years have gone by since the definitive detection of origin of GISTs. Research in the last decade was more focused upon the justification of imatinib mezylate therapy in GISTs and clarification why a secondary resistance that occurred during the kinase inhibitors therapy. The era of therapy for GISTs, targeting the primary activating mutations in the KIT proto-oncogene; is being proclaimed as bringing the message of special importance to the pathologist role in multidisciplinary team that are responsible for treating patients with locally advanced or metastatic GIST. This is the first conclusive message forthcoming from this book. On the other hand, the book provides summarised and case-based knowledge on current management of gastrointestinal and extragastrointestinal stromal tumours. We hope that this book may be considered as a worthwhile timely addition to clinical science dissemination, medical education, further basic and clinical research.

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