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SUPPLEMENT (SPECIAL ISSUE)

Adjuvant and neoadjuvant therapy for primary GIST

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Abstract Adjuvant therapy for primary GIST has proven benefit in extending disease free survival. Defined risk factors for recurrent disease are based on GIST size, location, and mitotic rate and provide useful guidelines for selecting patients for adjuvant therapy considerations. Neoadjuvant therapy with tyrosine kinase inhibition has potential usefulness in primary GIST, although not yet as standard of care. Advantages can include tumor downsizing to provide opportunity for less morbid surgical resection as well as to decrease risk of intra-op tumor rupture. These theoretical considerations have not been evaluated in large clinical studies.

Keywords Primary GIST · Adjuvant therapy · Neoadjuvant therapy · Tyrosinekinase inhibitors

Introduction

The multimodality management of gastrointestinal stromal tumors (GISTs) has evolved considerably since 2001 when the first patient with metastatic GIST was treated with imatinib (IM). The development of clinically effective tyrosine kinase inhibitors (TKIs) targeting the transmembrane receptor tyrosine kinase KIT revolutionized management of advanced (metastatic and unresectable) disease and provided an opportunity for adjuvant and neoadjuvant considerations for localized disease. To date, two tyrosine kinase inhibitors (TKIs) have been approved by the United States Food and Drug Administration for the treatment of advanced GIST: imatinib mesylate (Gleevec, Novartis Pharma, Basel Switzerland) for first line and sunitinib malate (Sutent, Pfizer Inc, New York, NY) for second line or IM intolerance. Recently, IM was approved for adjuvant use in patients with primary GIST following the results from the large American College of Surgeons Oncology Group (ACOSOG)-led randomized trial (Z9001) that showed significantly fewer recurrences of tumors in patients who received imatinib for 1 year after complete surgical resection compared to patients receiving placebo. This article reviews the scientific rationale for using TKI therapy in patients after surgery for resectable tumors and before surgery in patients with borderline resectable GISTs or in GISTs where anatomic location could result in en-bloc resection leading to excessive morbidity.

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Surgery in the pre-TKI era

In the pre-TKI era, surgery was the only known effective treatment for GISTs. Accordingly, surgical resection was applied to patients with both localized tumors and metastatic disease as there was no effective systemic therapy. Retrospective studies from single institutions with experience treating GISTs report that approximately half of patients present with localized disease and half of the patients present with advanced GIST, defined as metastatic or unresectable disease. The goal of surgery is to achieve a complete macroscopic resection with negative microscopic margins (R0 resection). Depending upon the GIST-bearing organ, exact tumor location, and tumor size, different surgical approaches are required. In general, primary tumors tend not to invade surrounding organs and wedge or segmental resection of the involved GI site is adequate. Lymph node metastasis are uncommon and lymphadenectomy

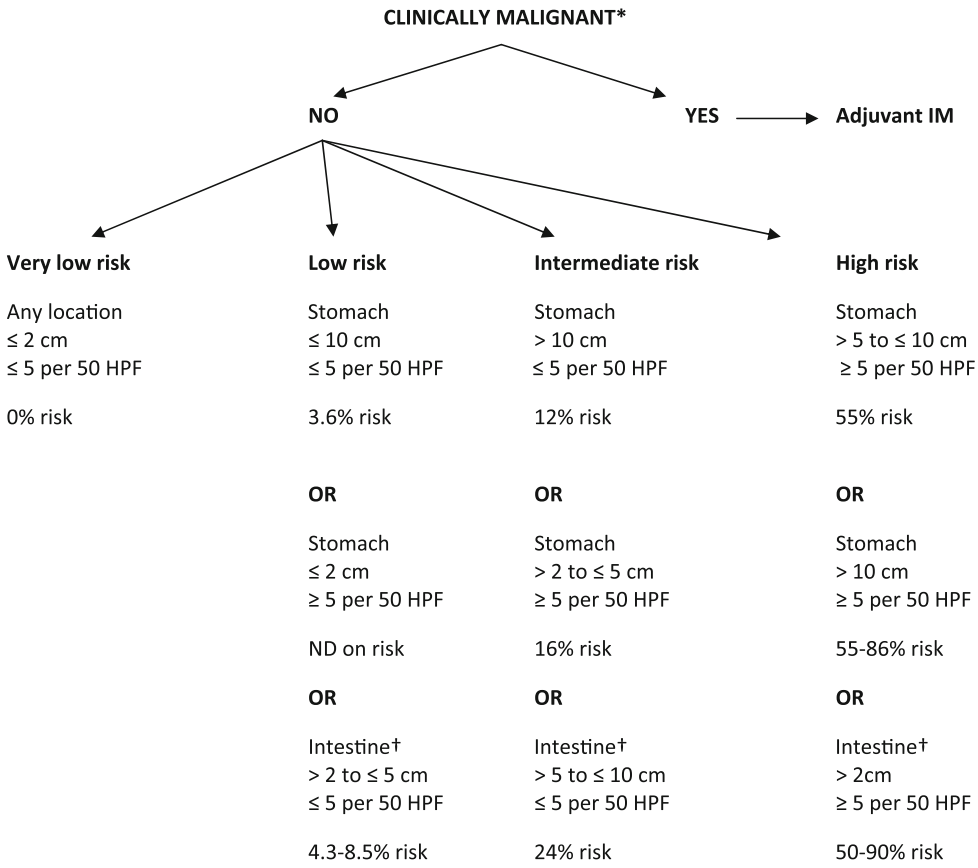

Fig. 1 Recurrence risk stratification after surgical resection based on intraoperative findings, tumor location, size and mitotic rate. *Clinically malignant refers to intra operative findings of peritoneal disease, tumor rupture, tumor invasion. †Intestine denotes duodenum, jejunum/ileum or rectum

unnecessary. There are no prospectively collected data available as to whether the extent of surgical resection margins correlate with risk of local or distant tumor recurrence.

Risk of recurrence following resection in the pre-TKI era

Surgical outcomes with GISTs reported prior to the TKI-era demonstrate the limitations of applying surgical oncologic principals to this tumor type. Despite a complete surgical resection with negative margins, local and distant recurrence occurs in up to 50% of patients and the overall survival rate at 5 years is approximately 50% for patients who undergo a complete resection. The median time to recurrence after surgery is 19–25 months. The first recurrence is typically in the abdomen with metastasis to the liver and peritoneal surfaces. Recurrences are often multifocal precluding and often not amenable to surgical resection [1–3].

In an attempt to define variables of surgical outcomes, a variety of surgery, tumor and pathology-related factors were identified from retrospective data to correlate with risk of recurrence. These factors included completeness of resection, tumor size and mitotic count. Additionally, the primary tumor site and c-kit mutational status allow for further risk stratification. All of these studies demonstrate that patients treated with R0 resection have significantly longer survival than those patients treated with incomplete (R2) resection [1–4]. In 2001, Fletcher and colleagues convened a GIST workshop with the goal of developing a consensus approach to estimating metastatic risk for primary tumors based on size and mitotic count [5]. The National Comprehensive Cancer Network (NCCN) endorsed the risk classification system proposed by Miettinen and Lasota of the Armed Forces Institute of Pathology based on long-term follow-up data from over 1900 GIST patients, which stratifies risk according to tumor size, number of mitoses per 50 high-power fields and tumor location [6]. Recently, additional variables linked to recurrence, group patients by the intraoperative findings of tumor rupture, invasion or peritoneal dissemination. These were subsequently added to the Fletcher system in an attempt to identify patients who may benefit from adjuvant IM [7]. These strategies can allow for predictive models of the level of risk for recurrence in individual patients (Fig. 1). With the limited success of the surgical approach to GISTs, novel treatments for this disease were clearly needed and came about through collaborative translational research efforts that now provide a paradigm for the future of specific targeted multimodality treatment of solid tumors.

The discovery of c-kit and the dawn of the TKI-era

Research efforts began with the hypothesis that GISTs originate from interstitial cells of Cajal (ICC) located in the myenteric plexus throughout the GI tract. In the early 1990s, ICC were found to express the cell surface receptor tyrosine kinase KIT and a phenotype of intestinal dysmotility was evident in mice treated with antibody that blocked KIT or in mice genetically deficient in c-kit [8, 9]. In 1998, based on the discovery of c-kit mutations in mast cell leukemia's [10, 11] Hirota and Kitamura identified mutations in the region between the transmembrane and tyrosine kinase domains of c-kit in five patients with GIST tumors [12] and correlated c-kit mutation status with prognosis in a larger cohort of patients with GIST [13]. Only a few years later, the therapeutic use of compound STI571, a selective small molecule inhibitor of the protein tyrosine kinases PDGFα, KIT and BCR-ABL fusion protein was reported in a case involving a patient with metastatic GIST refractory to multiple surgeries, conventional and experimental treatments [14]. Within weeks of starting STI571, the patient with treatment-refractory GIST exhibited an objective clinical response with a dramatic reduction in tumor volume.

TKI's for advanced GIST

These impressive early results led to the initiation of clinical trials in metastatic GIST testing the efficacy of IM (formerly STI571). Prior to IM, systemic chemotherapy with anthracycline-based regimes had response rates of only 5%, and GIST tumors were considered resistant to radiotherapy. With the addition of IM, approximately 85% of patients with metastatic GIST demonstrated a clinical benefit defined as partial response or stable disease with approximately 70% of patients alive at 2 years [15–17]. Based on these encouraging results and tolerable toxicities, IM was approved by the FDA in 2002 for the treatment of metastatic and/or unresectable GISTs.

Mutations in c-kit, or less commonly, platelet-derived growth factor alpha (PDGFα) can be identified in over 90% of GISTs [18]. Lessons learned from patients with metastatic disease revealed that c-kit mutational status correlated with response to IM [19]. In addition, it was learned that response to kinase-directed therapy is not maintained indefinitely and patients with a median time of 24 months develop disease progression through the acquisition of additional activating c-kit or PDGFα mutations in tumor clones rendering them IM refractory [20]. Initially for patients who developed progressive disease while on IM dose escalation can be attempted [21]. The introduction of another novel TKI, sunitinib, to IM-refractory GIST increased the median time-to-progression from 6 weeks in placebo-treated patients to 27 weeks in patients who received sunitinib. These results led to the second FDA approved TKI for IM refractory advanced GIST in 2006 [22, 23].

IM as an adjuvant to surgery

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 IM combined with complete surgical resection. Four large multi-institutional trials have evaluated the efficacy of standard dose adjuvant IM (400 mg/day) (Table 1). The American College of Surgeons Oncology Group (ACOSOG) sponsored two prospective trials evaluating adjuvant imatinib in completely resected, localized primary GIST. The ACOSOG Z9000 phase II trial evaluated recurrence and survival in 106 patients with high risk completely resected GIST ($\geq$10 cm, intraperitoneal rupture or bleeding, or multifocal tumors) treated with 1 year of adjuvant IM 400 mg/day. Safety results of this trial were reported at the American Society of Clinical Oncology Meeting in 2005. The ACOSOG Z9001 multicenter adjuvant trial was designed at the end of 2000, when fewer than 150 patients with metastatic GIST had been treated worldwide. The trial randomized completely resected patients with tumors $\geq$3 cm in size to 1 year of adjuvant IM (400 mg/day) versus placebo. In 2007, independent interim review found a statistically significant difference in relapse-free survival between treated and control group had been reached; because of this, the trial was unblinded. During the year of therapy, there was a 17% recurrence rate in the placebo group versus a 2% recurrence rate in the IM group [24]. Based on these positive results, 400 mg/day adjuvant IM received FDA approval in 2008 for GIST $\geq$3 cm.

The duration of adjuvant therapy remains controversial and was not specified in the FDA approval since the rate of recurrences in the Z9001 trial IM-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 noted after treatment interruptions in patients with metastatic disease [25]. Empirically, this would suggest that in a high risk primary GIST a longer duration of IM exposure may be necessary to prevent disease recurrence. Two large European adjuvant trials testing longer durations of adjuvant IM have met accrual goals and are maturing; the Scandinavian Sarcoma Group (SSG) and the German Arbeitgemeinschaft Internistische Onkologie (AIO) are jointly conducting a randomized Phase III trial to evaluate 1 year versus 3 years of adjuvant IM in patients with high risk tumors, and the European Organization for Research and Treatment of Cancer (EORTC) 62024 study

Table 1 Multicentric clinical trials of adjuvant imatinib

Study	Pts	Design	Endpoints	Inclusion/exclusion criteria	Current status
ACOSOG Z9000	*N* = 107	Nonrandomized, open-label All pts received 400 mg/d adjuvant imatinib for 1 year	Survival 2-year and 5-year recurrence rate Toxicity	Histol. confirmed primary KIT + GIST Tumor larger than 10 cm Tumor rupture, intraperitoneal hemorrhage Multifocal intraperitoneal tumors	Study completed in 2005 RFS at 1 year: 94% Follow-up at 4 years: OS 97%, RFS 61%,
ACOSOG Z9001	*N* = 713	Randomized, placebo controlled Patients either received 400 mg/d adjuvant imatinib or placebo	*Primary* Initially OS, later changed to RFS in *Secondary* OS Safety	Histol. confirmed primary KIT + GIST Larger than 3 cm Completely resected	Study completed Follow-up: 3 yrs 1-yrs RFS rate = 97% versus 83% $P = 0.0001$ 2-yrs RFS rate = 90% versus 71% 2-yrs OS rate = 92.3%
SSGXVII-AIO	*N* = 400	Randomized phase III Pts receive one year or three years of imatinib 400 mg imatinib daily	*Primary* RFS *Secondary* Safety and tolerability TTP, OS	Histol. confirmed primary KIT + GIST Completely resected (R0/R1) High risk according to consensus Tumor rupture	Study completed First analysis after 110 events (recurrence or death)
EORTC 62024	*N* = 906	Randomized phase III Pts receive 2 years of imatinib 400 mg/d or no treatment	*Primary* OS initially, changed to time to imatinib failure (TTIF) *Secondary* OS DFS OR (radiographic)	Histol. confirmed primary KIT + GIST Intermediate or high risk according to consensus Completely resected	Study completed Interim analysis expected on time to secondary resistance (TTSecRes)

compares 2 years of adjuvant therapy with observation. In this study due to crossover design with the expectation that IM-naïve patients receive benefit at recurrence, the primary endpoint was changed from overall survival to time to IM failure (TTIF) in an attempt to generate timely results. In the United States, a new trial (CSTI571BUS282) evaluating the adjuvant use of IM for 5 years postoperatively began accruing patients in June of 2009. These trial results will hopefully better define optimal treatment duration and reaffirm the benefit of adjuvant IM.

With FDA approval of adjuvant IM, surgeons must adhere to the oncologic principals of thorough exploration for distant spread and complete gross tumor removal. Intraoperative findings such as location of primary tumor site, tumor rupture, tumor bleeding and potential for peritoneal seeding should be described in the operative note. Pathologic assessment should include details of tumor size and mitotic number per 50 high-power fields. In consulting with patients after surgery, risk for recurrence can be estimated to allow an informed discussion of the potential prevention of recurrence with the adjuvant use of IM. If a cutoff of <10% risk of recurrence is a threshold to withhold adjuvant therapy in favor of observation and a risk of 30% is chosen to initiate adjuvant IM, the recommendation becomes more standardized. Patients with a gastric GIST of $\leq$2 cm regardless of mitotic rate, gastric GIST $\leq$10 cm and $\leq$5 mitoses/50 HPF and those with GIST of the duodenum, small bowel and rectum that are $\leq$5 cm with $\leq$5 mitoses/50HPF have been noted as low risk. Alternatively, patients considered high risk for recurrence should receive a strong recommendation for adjuvant IM treatment perhaps for longer than 12 months. The more difficult situation exists for patients that are in the intermediate-risk category for recurrence based on tumor site, size and mitotic rate. This includes patients with a large gastric GIST >10 cm with $\leq$5 mitoses/HPF (risk of 12%), or gastric GIST measured >2 cm but $\leq$5 cm with $\geq$5 mitoses/50HPF (risk of 16%) as well as small bowel GIST >5 cm but $\leq$10 cm with $\leq$5 mitoses/HPF (risk of 24%). In such patients, additional prognostic factors gleamed from intraoperative findings or mutational analysis may provide added information to this discussion [26]. Recently, a nomogram has been developed to assess risk recurrence [27].

The use of neoadjuvant IM for primary GIST

In patients with primary tumors in which the surgeon estimates that an R0 resection may be difficult to achieve, or may be easier to achieve if tumor cytoreduction were possible, therapy with neoadjuvant IM can be considered based on recommendations from both European and US guidelines [28, 29].

Locally, extensive GIST tend to be quite friable and hypervascular so that intraoperative manipulation may lead to tumor rupture and peritoneal seeding. A preoperative course of IM may be beneficial in decreasing this risk. In addition, there are other theoretical advantages to planned preoperative IM. The usefulness of solid tumor down-staging prior to surgery has long been a subject of clinical research. The advantage of size reduction of a GIST in the duodenum, rectum, esophagus, or esophago-gastric junction is perhaps the most important use of neoadjuvant IM and has the potential for decreasing the morbidity and mortality of a large surgical resection [30]. Another potential benefit for neoadjuvant application involves the effectiveness of combining the IM cytostatic effect with complete surgical resection for large GIST in an attempt to obviate the subsequent development of resistant GIST clones which are known to confound the long-term use of IM for metastatic disease. All of these considerations have yet to be tested in large prospective clinical studies. The only prospective multi-institutional neoadjuvant GIST trial to date was the RTOG 0132 study [31]. This trial established the safety profile of preoperative IM and the potential for successful down-staging of operable GIST. Anecdotal small series single institutional reports also support this concept [32, 33]. It is important, however, to note that in the setting of resectable GIST response to neoadjuvant IM must be evaluated early and continuously and surgical resection should be offered within a 3–6 month time due to concern for development of tumor progression. In addition, adjuvant IM should be continued postoperatively in high risk GIST. The advantages of neoadjuvant versus standard postoperative adjuvant for primary GIST relative to recurrence and survival has not been well defined and are theoretical; therefore, careful consideration for the particular clinical situation is necessary to determine the optimal recommendation.

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