Gastrointestinal Stromal Tumours: A 10 Year Multicenter Audit

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Abstract

Background: Gastrointestinal stromal tumours (GISTs) are unique neoplasms of the gastrointestinal (GI) tract. The development of targeted therapeutic agents such as imatinib mesylate (Glivec) has altered the way on how we now manage these rare malignancies. The aim of this study was to evaluate the management of GISTs in three Irish tertiary hospitals. Methods: We performed a retrospective, multicenter audit of patients diagnosed with gastrointestinal stromal tumours over a ten year period (2005-2015). Results: 110 patients were included in the study. Abdominal pain was the most common presenting symptom, reported in 30% of patients, while 31% were incidental findings. The stomach was the most common primary site of disease, observed in 77% of cases. 15 patients had metastatic disease at the time of diagnosis (14%), and 10 of these patients had liver involvement. More than half of patients (61%) were managed with surgical excision alone (61%), while 24% were managed with surveillance and 28 patients treated with adjuvant Glivec, which was generally well tolerated. 18 patients (20%) demonstrated recurrent or progressive disease after first line treatment. 102 patients (93%) are alive today. Conclusion: While surgery is widely regarded as the primary treatment modality for GISTs the addition of imatinib mesylate has enabled physicians to deliver more personalised treatment while optimising patient outcomes.

Keywords: gastrointestinal stromal tumour; GIST, KIT, imatinib mesylate, glivec

1. Introduction

Gastrointestinal stromal tumours (GISTs) are rare neoplasms, representing 1% of all primary GI cancers (Rubin et al. 2000; Miettinen & Lasota, 2001; Miettinen et al., 1999; Watson et al., 2016). Recent epidemiologic data from Sweden and Iceland report an incidence of 14.5 and 11 per million population, respectively, with a median age of diagnosis 66-69 years (Nilsson et al., 2005; Tryggestad et al., 2005). GISTs may be localised to any portion of the gastrointestinal (GI) tract, however they are most often found in the stomach (60%) and proximal portion of the small intestine (30%) (Rubin et al. 2000; Miettinen & Lasota, 2001; Miettinen et al., 1999; Watson et al., 2016). Diagnosis is often made incidentally, however patients may complain of nausea, vomiting, abdominal pain and weight loss (Ramnohan et al., 2013). Anaemia may also be observed due to tumour erosion (Rubin et al. 2000; Connolly et al., 2003).

Surgery is considered the primary treatment modality for primary, localised GISTs. However in those patients where the disease extends beyond the knife, prognosis is poor. Advances in our understanding at a molecular level led to the discovery that the mutational activation of the c-KIT oncogene is responsible for stimulating the growth of these cancer cells. This pivotal breakthrough has led to the development of novel treatment agents such as imatinib mesylate (Glivec), resulting in an increased median survival to 60 months (Watson et al., 2016; Otani et al., 2006).

2. Methods

We performed a retrospective, multicenter audit of patients diagnosed with gastrointestinal stromal tumours over a ten year period (2005-2015). 110 patients were identified using the Hospital InPatient Enquiry (HIPE) database
of three Irish tertiary hospitals. Clinical data was then retrieved from hospital pathology and imaging reports as well as patient records. Completed data templates from each centre were then merged into a single database. Unique patient identifiers were assigned to protect patient confidentiality. This database included clinical parameters pertaining to diagnosis, tumour characteristics and management.

3. Results

A total of 110 patients were included in the database. Median age of diagnosis was 63 years. Abdominal pain was the most common presenting symptom, reported in 30% (33/110) of patients, while 31% (34/110) were incidental findings (Figure 1). 21 patients (19%) presented with clinically significant anaemia or GI bleeding. Non-specific symptoms such as weight loss and anorexia were observed in seven cases. Other symptoms recorded include diarrhea (2 patients), gastroesophageal reflux (1 patient), belching (1 patient), and palpable abdominal mass (2 patients). In fourteen cases the presenting symptom was unknown.

![Figure 1. Clinical Presentation](image)

The stomach was the most common primary site of disease, observed in 77% of cases (85/110 patients) (Figure 2). 20 patients (18%) had small bowel GISTs. Other primary sites included the oesophagus (1 patient), large bowel (1 patient), pancreas (1 patient), rectum (1 patient) and pelvis (1 patient). 15 patients had metastatic disease at the time of diagnosis (14%), 10 of these patients had liver involvement.

![Figure 2. Site of Primary Tumour](image)

29 patients (26%) were at high risk of recurrence (Figure 3). 10 patients were intermediate risk (9%), 60 patients were low risk (55%) and 11 patients (10%) were classified as at a very low risk of recurrence.

24 patients were managed with surveillance alone. 23 of these patients were stratified as low risk. One patient in the high risk of recurrence group was not a surgical candidate due to comorbidities and managed with surveillance based on patient preference. Overall survival in patients managed with surveillance alone was 100%.
Figure 3. Patient risk groups according to risk stratification based on Miettinen & Lasota (Miettinen & Lasota, 2006)

56 patients underwent surgical excision alone (61%), with 4 patients undergoing neoadjuvant treatment with Glivec, all proceeding to surgery with a significant reduction in tumour burden. 28 patients were treated with adjuvant Glivec at the standard dose of 400mg.

18 patients (20%) demonstrated recurrent or progressive disease after first line treatment. 4 patients recurred after surgical excision alone, and of these 2 were managed with resection while the remaining two patients were commenced on adjuvant Glivec with response. 9 patients had recurrent disease after the recommended 3 years of adjuvant therapy, and were re-challenged with Glivec with response. 6 patients progressed on adjuvant Glivec and received second line Sunitinib. Five of these patients progressed and ultimately required third line treatment. One patient was managed with a Glivec rechallenge. Two patients received Regorafenib, one of which continued to progress and also received Sorafenib. One patient received Temsirolimus. Third line treatment for one patient was unknown.

In general treatment was well tolerated, however two patients reported symptoms of Glivec-induced congestive heart failure which was navigated with a treatment break. Diarrhoea was also reported (1 patient), and again resolved after a short treatment break. Palmar plantar erythrodysesthesia was observed in one patient on Sunitinib.

102 of our patients (93%) are alive, while one patient died due to progression of disease. Seven patients were lost to follow up.

4. Discussion

Mesenchymal tumours are common benign soft tissue neoplasms that may affect the GI tract (Rubin et al., 2000; Watson et al., 2016; Connolly et al., 2003). GISTs represent a subset of this family and may be found in any portion of the GI tract as observed in our patients, however they are most commonly localised to the stomach (60%) and proximal portions of the small intestine (30%) (Rubin et al. 2000; Miettinen & Lasota, 2001; Miettinen et al., 2001; Watson et al., 2016).

Most cases are the result of sporadic mutations, however familial GISTs have been described, and appear to be associated with earlier development and increased number of GISTs (Miettinen et al., 2001; Goettsch et al., 2005; Janeway et al., 2007; Miettinen et al., 2006). We recorded one patient with this familial form, presenting with a GIST localized to the stomach at age 60 with two recurrences, both successfully managed with resection.

GISTs are thought to derive from the interstitial cells of Cajal (ICC), which display features of both smooth muscle and neuronal differentiation (Sircar et al., 1999). Their main function is to initiate and coordinate peristalsis, thus giving them their sobriquet ‘GI pacemaker cells’. These cells express the cell surface marker CD117, or c KIT, a transmembrane receptor protein kinase with a role in regulating cellular proliferation and differentiation.

In 1998 Hirota and colleagues revealed that GISTs are caused by gain-of-function mutations in c-KIT (Hirota et al., 1998). This results in a continuously activated tyrosine kinase, leading to uncontrolled cellular proliferation and resistance to apoptosis. Approximately 90% of GISTs express KIT on their cell surfaces (Rammohan et al.,
GISTs are often incidental findings, as observed in the current study. Non-specific signs and symptoms such as nausea, vomiting, abdominal discomfort and weight loss may be presenting features. Abdominal pain was the principal complaint in our study. Haematemesis, melaena or anaemia (observed in 19% of our patients) may also occur due to erosion into the GI lumen.

Contrast enhanced computed tomography (CECT) remains the diagnostic imaging procedure of choice for identifying GISTs, while endoscopic ultrasound (EUS) may be used to facilitate fine needle aspiration (FNA).

GISTs have the potential to metastasise; however criteria for identifying those that may exhibit more aggressive behaviour have been debated for many years (Rammohan et al., 2013; Miettinen & Lasota, 2006; Burkill et al., 2003). The NIH 2002 consensus was used to stratify patients according to risk of recurrence, considering tumour size and mitotic rate as predictors of recurrence (Flethcher et al., 2002). In 2008 Joensuu added tumour rupture to the risk assessment (Joensuu, 2008). GISTs arising in the intestinal tract have been shown to be more aggressive than those arising in the stomach, with tumour related mortality 17% in gastric tumours versus 39% in small bowel GISTs (Miettinen et al., 2005; Miettinen et al., 2006). Three large retrospective studies from the Armed Forces Institute of Pathology (AFIP) added anatomical origin as an additional risk factor (Miettinen & Lasota, 2006)(Table 1). This addition was supported by DeMatteo et al. (2000), who also added tumour size and mitotic rate (DeMatteo et al., 2000) as independent risk factors. The more recent phase III adjuvant imatinib trial, ACOSOG Z9001, also reported poorer long term outcomes in those patients with tumours arising from the small bowel (Corless et al., 2014).

Table 1. Risk Stratification of Primary GIST by Mitotic Index, Size and Site. HPFs (High power fields) (Adapted from Miettinen & Lasota, 2006)

<table>
<thead>
<tr>
<th>Mitotic Index</th>
<th>Tumour size</th>
<th>Gastric</th>
<th>Duodenum</th>
<th>Jejunum/Ileum</th>
<th>Rectum</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;= 5 per 50 hpf</td>
<td>&lt; 1 cm</td>
<td>None (0%) Very low (1.9%) Low (3.6%) Moderate (10%)</td>
<td>None (0%) Low (8.5%) Insufficient data High (34%)</td>
<td>None (0%) Low (4.5%) Moderate (20%) High (52%)</td>
<td>None (0%) Low (8.5%) Insufficient data High (57%)</td>
</tr>
<tr>
<td>&gt; 5 per 50 hpf</td>
<td>&lt; 1 cm</td>
<td>None (0%) Moderate (10%) High (55%) High (88%)</td>
<td>Insufficient data High (20%) Insufficient data High (84%)</td>
<td>High (73%) High (85%) High (90%)</td>
<td>High (54%) High (52%) Insufficient data High (71%)</td>
</tr>
</tbody>
</table>

Tumour features associated with higher risk of metastasis include size > 5cm, lobulated appearance, heterogeneously enhance on imaging, with mesenteric fat infiltration, ulceration, regional lymphadenopathy or an exophytic growth pattern on CT (Choi et al., 2007).

Prior to 2001, surgery was the only available treatment for GISTs. In cases where complete resection is not achieved, prognosis is poor, with median survival ranging from 10-23 months (DeMatteo et al., 2000). The addition of imatinib has revolutionised treatment in both the adjuvant and neoadjuvant setting, increasing median overall survival to 60 months (Otani et al., 2006).

Imatinib mesylate (Glivec) is a tyrosine kinase inhibitor (TKI) that is structurally similar to adenosine triphosphate (ATP). By competitively binding to the ATP binding site of the target kinases, it can prevent substrate phosphorylation and signaling, ultimately inhibiting tumour growth (Beham et al., 2012, Pidhorecky et al., 2000; Sepe et al., 2009).

The addition of imatinib in the adjuvant setting has been shown to improve PFS (Progression Free Survival) and OS (Overall Survival) (DeMatteo et al., 2009; Casi et al., 2013; Joensuu et al., 2012). Data from the Scandinavian Sarcoma Group (SSG) XVIII trial has also shown at least 36 months of adjuvant imatinib is the recommended duration of treatment for patients with an intermediate or high risk of recurrence (Flethcher et al., 2002; Joensuu et al., 2012).
Imatinib may also be considered in patients with widespread metastatic disease or recurrence post resection. Metastasis to the liver is frequently seen, and was observed in 10 of our patients. Lung metastasis is rare, but was observed in two of our patients. TKIs have been shown to slow growth in approximately 80% of patients, however complete metabolic responses are rare (Carboni et al., 2003; Chacon et al., 2005; Bauer et al., 2005).

Imatinib is well tolerated and this was also reflected in our audit. The most common side effects reported in the literature include fluid retention, GI complaints such as altered bowel habits and nausea, and fatigue. These effects are usually mild however and rarely warrant treatment discontinuation (Watson et al., 2016). Congestive heart failure has been noted in 8.2% of patients, and was reported in two of our patients. Arrhythmias and acute coronary syndromes are rare (Rammohan et al., 2013). Generally symptoms subside if imatinib is temporarily discontinued (Watson et al., 2016).

Alternative therapeutic options for patients who have progressed on imatinib include sunitinib, regorafenib and clinical trials. Re-challenging patients with imatinib in those who previously benefited from it has also been shown to be effective. This was reflected in our study with 9 patients responding after Glivec re-challenge (Kang et al., 2013).

GISTs are most likely to recur within the first 5 years, and guidelines from NCCN suggesting CT imaging every 3-6 months for 5 years, and annually thereafter (Sepe et al., 2009). In patients with advanced disease routine follow up with imaging is recommended every 3-6 months.

Conflict of Interest

Dr. Geoff Watson declares that he has no conflict of interest
Dr. D. Kelly declares that she has no conflict of interest
Dr. J. Greene declares that he has no conflict of interest
Dr. E. Malone declares that he has no conflict of interest
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Dr. C.M. Kelly declares that she has no conflict of interest
Prof. R. McDermott declares that he has no conflict of interest
Prof. J. McCaffrey declares that he has no conflict of interest

Ethical Approval

This article does not contain any studies with human participants or animals performed by any of the authors.

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