A USA registry of gastrointestinal stromal tumor patients: changes in practice over time and differences between community and academic practices

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on behalf of the reGiSTry Steering Committee

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Background: The objective of the study was to describe patterns of care of patients with gastrointestinal stromal tumors (GISTs) in the United States in the tyrosine kinase inhibitor (TKI) era.

Patients and methods: From November 2004 through March 2009, data were collected regarding demographics, diagnostic history, treatment, relapse, and survival of 882 patients with GIST from 122 community and academic medical practices.

Results: The most common first-line treatment for the 719 patients presenting with localized GIST was surgery (87%). Use of adjuvant imatinib increased after June 2007; 47% of patients enrolled in the registry considered by the investigator to be at high risk for recurrence received adjuvant imatinib after June 2007 versus 18% before. Overall, 56% of patients received imatinib and 11% received sunitinib. The utilization of targeted therapy increased over time (45% and 0.4% of patients received imatinib and sunitinib, respectively, in 2006 versus 56% and 11%, respectively, in 2009).

Conclusions: These are the first GIST registry data from the TKI era. The use of targeted therapy for GIST has increased in accordance with updated treatment guidelines. Diagnosis of GIST has evolved with increased use of KIT testing. The duration of targeted therapy in the adjuvant therapy setting is similar in community and academic practices.

Key words: gastrointestinal stromal tumors, registry, survival, tyrosine kinase inhibitor

introduction

Although only ~5000 new cases of gastrointestinal stromal tumors (GISTs) are diagnosed annually in the United States [1], GISTs are the most common mesenchymal neoplasms of the gastrointestinal tract, characterized by gastrointestinal primary disease, a unique histological morphology, and expression of the KIT protein [2, 3].

Consensus recommendations for the treatment of GIST were developed by the National Comprehensive Cancer Network in 2007 [4] and updated in 2010 [1]. These recommendations include the following: consideration of adjuvant targeted therapy in patients at significant risk for recurrence, neoadjuvant therapy if surgical morbidity would be reduced by shrinking the primary tumors preoperatively, use of mutational analysis to detect exon 9 mutations, to consider starting imatinib at 800 mg if an exon 9 mutation is present, and use of sunitinib as second-line therapy [1].

However, despite the guidelines, little is known about patterns of care and outcomes of GIST patients treated in the community, nor about how well consensus guidelines are being followed. Previous articles describing the natural history of GIST in patients followed long term were mostly single-institution reports with relatively small numbers of patients [5, 6]. Given the small numbers of GIST patients diagnosed annually and treated in any single practice, prospectively gathered registry data on GIST patients treated across the United States offer the best hope of understanding how GIST patients are being treated and the results of those treatments. There have been no reports of prospectively gathered registry data describing the management of large numbers of GIST patients, much less data documenting how variations in management by patient or provider characteristics affect outcomes.
The reGISTry is an observational database initiated in 2004 to understand the management of patients with GIST in the United States. For the present study, we used the reGISTry database to analyze methods of diagnosis and disease assessment, treatment patterns, and treatment responses in GIST patients over time.

patients and methods

participating sites and patients

Participating USA sites were identified through advertisements in medical journals and GIST patient Web sites. Sites were categorized based on size and type of institution (e.g. community practice, university/academic medical center). All patients diagnosed with GIST who were currently being treated or followed at each site were eligible for enrollment.

reGISTry database

The reGISTry database was designed to be active for at least 7 years with an anticipated total enrollment of 1800 patients and individual follow-up of at least 1 year. Enrollment began in November 2004 and is ongoing. The reGISTry followed the recommendations of the Declaration of Helsinki. The protocol for enrollment of patients and use of data was approved by the institutional review board of each participating institution. Written informed consent was provided to Novartis for appropriate reGISTry-required interventions or procedures required. Site personnel entered specified data gathered at scheduled patient visits. The reGISTry used electronic data capture through a secure Internet-based portal (www.gistregistry.net) developed and maintained by Covance Inc.

For each patient, the reGISTry collected data on demographics (date of birth, sex, ethnicity), diagnostic history [date of GIST diagnosis; clinical presentation; diagnostic tests (including biopsy and imaging) carried out with results; location, size, and mitotic count of primary lesions and locations of metastatic lesions; results of any mutational analyses; family history], treatment [surgery, chemotherapy/targeted therapy (drugs, doses, duration, timing relative to surgery)], treatment referrals (all types), and dates of relapse or progression of disease. In addition, data regarding medical resource utilization and death (date and primary cause) were collected. Information regarding treatment management decisions, including the basis for the initial treatment decision, treatment management decisions criteria for choice of surgery or targeted therapy as the first course of treatment, assessment of patient response to targeted therapy [including computed tomography (CT) and positron emission tomography (PET)], and changes in therapy was also collected.

No adverse events were collected as part of the reGISTry. However, descriptions of serious adverse events causally related to a Novartis drug that occurred on or after 1 April 2008, and after the patient had signed informed consent were provided to Novartis for appropriate documentation and investigation.

data analysis

For this study, we extracted data on demographic and clinical characteristics, diagnostic and treatment history, and outcomes carried out every 6 months. Descriptive statistics were used to summarize collected data. The frequencies of use of different tests and treatments were calculated for the overall population, by type of provider (community or university/academic center), and by extent of disease at diagnosis.

results

A total of 122 sites located throughout the United States participated and 105 have enrolled patients (Appendix 1). The first patient was enrolled in November 2004. As of March 2009, there were 882 patients enrolled in the registry. One hundred nine patients were no longer actively contributing data to the registry, including 64 who died. Other reasons for discontinuation were primarily administrative (lost to follow-up, transfer of care, etc.).

The majority of participating sites (83%) were community-based practices that enrolled five or more subjects each. University/academic centers accounted for 17% of participating centers and 44% of subjects. The majority of patients were treated at the center where they were diagnosed regardless of the type of practice (60% and 61% of patients at community-based and university/academic centers, respectively). Forty percent and 39% of patients at community-based practices and university/academic centers, respectively, were referred to other practices/centers.

Table 1 summarizes patient characteristics. The patients’ median age was 62 years at the time of enrollment (range, 18–92 years), and 50% of patients were men. The mean time from diagnosis to entry into the registry was 1.9 years. However, the percentage of patients enrolled within 60 days of a GIST diagnosis increased from 15% when data were analyzed in 2006 to 22% when data were analyzed through 2009.

diagnosis

GIST was the original diagnosis in the majority of patients (n = 787; 89.2%). CT was the most commonly used initial diagnostic imaging method (76% of patients), followed by endoscopy (24%) and ultrasonography (12%). PET (3%) and combined CT–PET (3%) were rarely used for diagnosis. Immunohistochemical analysis to detect KIT was carried out.

<table>
<thead>
<tr>
<th>Variable</th>
<th>All</th>
<th>Community practice</th>
<th>Academic center</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of centers/practices</td>
<td>122</td>
<td>101</td>
<td>21</td>
</tr>
<tr>
<td>No. of patients</td>
<td>882</td>
<td>493</td>
<td>389</td>
</tr>
<tr>
<td>Median age at enrollment (range), years</td>
<td>62 (18–92)</td>
<td>65 (21–92)</td>
<td>60 (18–92)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>445 (50)</td>
<td>247 (50)</td>
<td>198 (51)</td>
</tr>
<tr>
<td>Female</td>
<td>437 (50)</td>
<td>246 (50)</td>
<td>191 (49)</td>
</tr>
<tr>
<td>Race, n (%)</td>
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</tr>
<tr>
<td>Caucasian</td>
<td>684 (78)</td>
<td>392 (80)</td>
<td>292 (75)</td>
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<tr>
<td>African American</td>
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<td>66 (13)</td>
<td>63 (16)</td>
</tr>
<tr>
<td>Asian</td>
<td>26 (3)</td>
<td>11 (2)</td>
<td>15 (4)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>25 (3)</td>
<td>13 (3)</td>
<td>12 (3)</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>18 (2)</td>
<td>11 (2)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Time from diagnosis to enrollment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range), years</td>
<td>0.85 (0–15.4)</td>
<td>0.85 (0–12.8)</td>
<td>0.83 (0–15.4)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>1.9 (2.38)</td>
<td>1.9 (2.39)</td>
<td>1.9 (2.37)</td>
</tr>
</tbody>
</table>

SD, standard deviation.
in 94% of patients, and 98% of these patients’ tumors were found to express the protein. Mutational analysis was carried out in only 6% of patients, including 12% of patients enrolled at academic centers but only 1% of patients enrolled at community-based practices.

Although surgery was used for diagnosis in 75% of patients overall, endoscopic fine-needle aspiration (FNA) was used in a greater percentage of patients (20%) diagnosed in 2009 than in 2006 (14%). Of 179 patients who had endoscopic FNA, 77 (43%) had ultrasound-guided procedures, whereas 102 (57%) did not. When surgical biopsy was carried out, it was usually part of, or intrinsic to, resection of the primary tumor (75%) or was an excisional biopsy (defined as macroscopically complete tumor removal without a specific or deliberate attempt to achieve microscopically negative surgical margins; 12%). Other reasons for surgical biopsy were incisional biopsy, intraoperative FNA or core biopsy, or resection of metastatic sites, each carried out in a minority of patients.

The most frequent sites of primary lesions were the stomach and small intestine (54% and 28%, respectively), followed by lesions in the colon, rectum, omentum, and peritoneum. The majority of patients (n = 719; 82%) were diagnosed with localized disease and 18% (163) with metastatic disease. The extent of disease at diagnosis did not change from 2006 to 2009.

To date, 311 patients have developed metastatic disease. The distribution of sites of metastases was similar in the 163 patients with metastasis at diagnosis and in the 148 patients with localized disease at diagnosis who developed metastatic disease. The most common sites of metastases in the latter group were the liver and peritoneum (Figure 1).

** treatment**

The most common first-line treatment for the 719 patients with localized GIST at diagnosis was surgery (87%) or targeted therapy (11%). To date, 21% of these patients have had disease recurrence. Data regarding histological assessment of tumor margins were not collected. The median time to local recurrence following first-line surgery for localized disease increased from 13.9 months (range, 12.5–73.6 months) in 2006 to 28.5 months (range, 0.2–118.5 months) in 2009. This suggests that the increased use of targeted agents is at least delaying, if not preventing, the onset of recurrence. However, the percentage of patients with distant disease recurrence and the time to distant recurrence did not change substantially over time. In 2006, 13% (19) of patients had distant recurrence at a median of 19.6 months following first-line surgical resection of the primary tumor; in 2009, 15% of patients (93) had distant recurrence at a median of 21.5 months (range, 0.7–114.5 months).

Of the 882 patients in the registry, 43 (5%) received neoadjuvant therapy with imatinib mesylate (Gleevec or Glivec; Novartis Oncology, East Hanover, NJ), including 12 patients with metastatic disease at diagnosis. At the time of data cut-off, three patients were continuing neoadjuvant imatinib before surgery. The median duration of neoadjuvant therapy in the 40 patients who had discontinued imatinib at the data cut-off for this analysis was 4 months (range, 0.2–17.1 months).

Before June 2007 (when positive results of an adjuvant imatinib trial were presented at the American Society of Clinical Oncology annual meeting) [7], 18% of GIST patients considered by the investigator to have a high risk for recurrence were treated with adjuvant imatinib compared with 47% after June 2007. Overall, 154 patients (17%) have received imatinib as adjuvant therapy. The median duration of imatinib in the 64 patients (combined academic and community practices) who were still receiving adjuvant imatinib at the data cut-off was 255.0 days (range, 0–2694 days). The median duration of adjuvant imatinib in the 39 patients in community practices who were still receiving imatinib therapy was similar, at 266.0 days (range, 1–2694 days). The median duration of imatinib in the 90 patients (combined academic and community practices) who had discontinued adjuvant therapy at the data cut-off was 337.5 days (range, 2–1970 days). In the 41 patients in community practices who discontinued adjuvant imatinib therapy, the median duration of treatment was similar (330.0 days; range, 2–1970 days). Among patients who had or were receiving adjuvant imatinib, the most recent status was no recurrence of disease in 68% (105), responding in 8% (13), progressing/mixed in 5% (8), and unknown, dose titration, or missing in 28 (18%) patients.

The primary method used to determine the efficacy of targeted therapy was size assessed by CT (69% in 2002 to 64% in 2008) (Figure 2). The use of CT size/density increased between 2002 and 2008 and the use of PET, although low, increased incrementally over the same time period.

The initial treatment for patients presenting with metastatic disease has changed since the initial analysis of the data. Overall, 50.3% of patients have undergone surgery as first treatment. However, a lower percentage of patients with metastatic disease are now undergoing surgery (55% in 2006 versus 50% in 2009) as their first intervention; instead, a greater percentage of patients are receiving targeted therapy (39% in 2006 versus 47% in 2009). Targeted therapy was the first treatment in 76 of 77 patients in the registry who received systemic treatment as first therapy for metastatic disease. In
2009, 53% of patients (44) with metastatic disease underwent surgery as frontline treatment in the community versus 47% (35) in academic practices.

Systemic therapy (cytotoxic chemotherapy or targeted therapy) was administered at some time during treatment to 794 of the 882 patients in the registry. Use of targeted therapy has increased since the initial data analysis. As of the 2009 data cut-off, targeted therapy consisted of imatinib mesylate, administered to 491 patients (56%) in the registry, and sunitinib malate (Sutent; Pfizer, New York, NY), administered to 260 patients (30%) in the registry versus 45% and 0.4% of patients, respectively in 2006 (Table 2). The majority of patients (90%) who received imatinib were treated with 400 mg/day at some point, with fewer patients receiving 600 or 800 mg/day (20% each, the combined percent is >100% since patients may have had more than one regimen at some point in time). Of the 97 patients who received sunitinib, 75% received 50 mg/day at some point (in a regimen of 4 weeks on, 2 weeks off), and 32% received 37.5 mg/day.

The best responses reported for patients who received imatinib or sunitinib for any reason are summarized by dose in Table 3. It is not possible to compare response rates or draw conclusions regarding the two targeted therapies as treatments may have been given at any time during the course of the disease (neoadjuvant therapy, adjuvant therapy, or first- or second-line therapy for metastatic disease) and these data are retrospective and treatment compliance was not assessed. Use of higher doses of either targeted therapy (e.g. imatinib 800 mg) may have been reserved for second- or third-line treatment of metastatic disease, accounting for the higher rates of progressive disease reported for higher doses.

**discussion**

Registry data can be particularly effective in providing information on the natural history and patient management strategies for rare tumors such as GIST. The data presented here are the first GIST registry data collected during the tyrosine kinase inhibitor (TKI) era. Patient enrollment (November 2004 through March 2009) into the reGISTry followed the USA Food and Drug Administration approval of imatinib (2 February 2002) and sunitinib (26 January 2006) and longitudinal analysis provides a mean to evaluate trends in patient care over time and across different care settings. Unlike previous GIST registries [6, 7], which were limited to patients in western Sweden and Iceland diagnosed before 2000 and 2003, respectively, the patients in the reGISTry were treated after the introduction of TKIs.

The introduction of TKIs for GIST has had a profound effect on response rates and survival among patients with unresectable or metastatic disease [7–14]. In a study of 147 patients with unresectable or metastatic disease, treatment with imatinib 400 or 600 mg daily yielded an overall response rate of 68.1%, with an estimated median overall survival of 57 months [8]. The inclusion of new treatments into clinical practice often occurs rapidly for cancers, particularly those with a poor prognosis or few treatment options, and is often based on promising evidence from clinical trials that have been presented only in abstract form. The use of imatinib as adjuvant therapy for GIST increased following the presentation of data from...
a large prospective multicenter study (American College of Surgeons Oncology Group Z9001 study) at a national meeting in June 2007 [7]. The adoption of adjuvant imatinib occurred across community and academic centers before peer-reviewed publication of these data in 2009 [14]. When the data were published in 2009, they showed that adjuvant imatinib administered for 1 year produced marked improvements in recurrence-free survival at 1 year (imatinib 98% versus placebo 83%; \( P < 0.0001 \)). At the time of publication, there was no difference in overall survival (\( P = 0.47 \)). Overall survival was difficult to calculate in this adjuvant study for a number of reasons including fairly short follow-up time, durability of responses, crossover design, option to cross over at interim analyses, possibility of curative surgery after a local recurrence, and secondary TKI therapies. Longitudinal analyses of prospectively collected data from the reGISTry may provide insight into survival rates as more data are added.

This study pointed out several differences between clinical practice and clinical practice guidelines such as those by National Comprehensive Cancer Network (NCCN) [1] and European Society of Medical Oncology (ESMO) [15]. Although the majority of patients had GIST as the original diagnosis, there was poor utilization (6%) of \( KIT \) mutation testing of tumors despite \( KIT \) mutation testing being a standard practice at several academic centers and is recommended by both NCCN [1] and ESMO [15]. This may be due to limited access to centers where testing is carried out, a lack of knowledge of the benefits of the testing, or possible differences in approach to patients with GIST treated with imatinib. Differences in response rates among reGISTry patients may also be attributed to differences in dosing patterns and treatment compliance in the ‘real-world’ versus clinical trial setting.

Iterative analyses of the registry data will allow for comparison of management patterns as treatments for GIST evolve. Areas of particular interest for future analyses include adoption of new treatment practices, use of mutational analysis to guide choice of therapy, evaluation of sunitinib in a continuous daily dosing schema for patients who develop resistance to imatinib, and use of CT-generated data about the size and density of tumors to accurately evaluate response to therapeutic interventions.

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disclosure

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references


appendix 1

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