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ORIGINAL RESEARCH

Comparison of the Long-Term Risk of Recurrence and Other Clinical Outcomes in GIST Patients Receiving Imatinib as Adjuvant Therapy—A Retrospective Chart Extract-Based Approach

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Abstract
Purpose To compare characteristics of patients, the risk of recurrence, and mortality among adult patients with primary resectable gastrointestinal stromal tumor (GIST) receiving short-term (6–12 months) versus long-term (≥24 months) imatinib therapy.
Methods Detailed information on primary resectable KIT-positive GIST patients initiated on imatinib adjuvant therapy was retrospectively collected for short- and long-term imatinib patients from 318 US oncologists using an online data collection form. Patient characteristics were compared using Wilcoxon and Chi-square tests. Disease recurrence and mortality rates were compared using multivariate Cox proportional hazard models.
Results Among the 406 short-term and 406 long-term imatinib patients, the median follow-up was 916 and 970 days, respectively. While patients generally had similar demographic characteristics, the short-term group had a higher prevalence of cardiovascular and ischemic heart diseases and patients in the long-term group had a higher pre-surgery risk profile. This finding was consistent with the main reason reported by oncologists for prescribing adjuvant imatinib over longer duration, i.e., patient risk profile. Disease recurrence [5.9 versus 1.2 %, ($p<.001$)] and mortality rates [7.1 % versus 2.0 %, ($p<.001$)] were higher in short- versus long-term patients. The adjusted risk of recurrence was 5.30 times ($p<.001$) higher, and mortality risk was 4.02 times ($p<.001$) higher in short- versus long-term patients.
Conclusions Patient risk profile is an important factor in oncologists' decisions to prescribe adjuvant imatinib. Despite the higher risk profile observed in long-term patients, the long-term use of imatinib was associated with a reduction in long-term risk of disease recurrence and mortality.

Keywords Gastrointestinal stromal tumors · GIST · KIT · KIT inhibitors · Imatinib · Soft tissue sarcomas · Sarcomas

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Background

A gastrointestinal stromal tumor (GIST) is a type of soft-tissue sarcoma that usually develops in cells within the wall of the stomach or intestines. GISTs may result from the over-expression or activation of mutation in KIT (CD117) protein or platelet-derived growth factor receptor alpha which provides a stimulus for tumor cell proliferation [1, 2]. The incidence of a GIST is estimated to be approximately 3,000–6,000 cases per year in the US [3, 4]. Most common GISTs sites are stomach (60 %), jejunum and ileum (30 %), duodenum (5 %), and colorectum (<5 %) [5, 6]. Approximately 20 % to 25 % of gastric GISTs and 40 % to

50 % of small intestinal GISTs are found to be malignant [6].

The standard of care in GIST management varies depending on the stage of the tumor, the presence of metastases, and the patient's risk profile. Tumor resection with clear margins remains the mainstay of treatment for localized primary resectable GISTs. However, a large proportion of patients may develop recurrent/metastatic disease even after curative surgery [7]. A recent study reported that more than 50 % of patients undergoing surgery relapse within 5 years [8, 9]. The introduction of tyrosine kinase inhibitors with imatinib (Gleevec® Novartis Pharmaceuticals) has changed the treatment landscape by increasing disease-free survival in GIST patients. Currently, imatinib is approved as adjuvant therapy following surgery and in adults with KIT-positive unresectable and/or metastatic malignant GIST [10]. Although initial approval was based on improvements in recurrence-free survival (RFS) following 1 year of imatinib treatment compared with a placebo, a recent multicenter, prospective, randomized Phase III study comparing 3 years versus 1 year of adjuvant imatinib showed superior clinical outcomes among patients receiving imatinib for 3 years [11]. RFS for patients receiving 3 years of adjuvant imatinib at years 3 and 5 were 88.1 % and 67.4 % versus 62.1 % and 50.3 % for patients receiving 1 year of adjuvant imatinib (hazard ratio [HR] 0.46, 95 % CI, 0.31–0.65, $p<0.0001$). Similarly, overall survival at years 3 and 5 was higher for patients on 3 years imatinib adjuvant compared with patients on 1 year adjuvant (96.3 % and 92.0 % versus 94.0 % and 81.7 %) (HR of 0.45, 95 % CI, 0.22–0.89, $p=0.019$) [11]. Based on these findings, the National Comprehensive Cancer Network (NCCN) panel of experts recommended in the 2012 NCCN Guideline to consider adjuvant imatinib for at least 36 months in high-risk patients [12].

To date, there are no specific guidelines on the optimal duration of adjuvant imatinib following GIST resection. Although long-term imatinib use has been shown to be beneficial in clinical trials, there is limited information on the imatinib treatment duration, risk of disease recurrence, and clinical outcomes in GIST patients undergoing treatment with adjuvant imatinib in a non-trial setting. The objective of this study was to compare characteristics of GIST patients and the risk of recurrence and survival among primary resectable GIST patients receiving short-term (6–12 months) versus long-term (≥24 months) imatinib adjuvant therapy in clinical practice.

Methods

Data Source and Sample Selection

Data were collected from patient charts via a physician-administered online data collection form. A survey/chart extraction form was developed specifically for this study. Oncologists and sarcoma specialists were recruited from a panel of over 200,000 medical professionals in the United States from a vendor specializing in online physician surveys. Physicians were invited by E-mail to participate in the study and to provide clinical information for a maximum of five patients who met the study selection criteria. Patients were randomly selected by physicians from a list of their eligible patients. Physicians were requested to consider only patients for whom they had complete clinical GIST-related information for at least 2 years following imatinib initiation. If a patient died within 2 years following imatinib initiation, all clinical information up until the time of death was collected. Patients were considered to be eligible for this study if they met the following criteria: (1) age of 18 years or older; (2) diagnosis of primary resectable KIT-positive GIST (CD117) and underwent surgery as primary treatment on or after 12/19/2008[1]; (3) no evidence of metastases prior to surgery and no evidence of residual macroscopic disease after surgery; (4) initiation of imatinib adjuvant therapy within 12 weeks following surgery date followed by continuous imatinib use for at least 6 months (no treatment gap >60 consecutive days); and (5) no use of other c-KIT inhibitors (imatinib or sunitinib), biologics, chemotherapy, or radiation therapy prior to imatinib initiation.

Based on imatinib treatment duration, patients were classified into two mutually exclusive cohorts: (1) short-term imatinib use (short-term group): treated with imatinib continuously for at least 6 months but no more than 12 months; and (2) long-term imatinib use (long-term group): treated with imatinib continuously for at least 24 months. In order to measure the impact of the short-term use versus long-term use of imatinib, patients in the short-term group who had a recurrence within the first 12 months—if they were still on imatinib—were excluded as the recurrence could not be attributed to the treatment interruption. Similarly, patients in the long-term group who had a disease recurrence within the first 12 months were excluded as these patients experienced a recurrence before they could benefit from the long-term imatinib use.

Data Collection

A data collection form was designed to collect patient/clinical information via a physician survey/chart extraction. First, physicians were asked to record information on their practice, general opinions regarding GIST treatment including role of risk profile in treatment decisions, and imatinib treatment initiation, duration, and discontinuation. Next, physicians were requested to record detailed clinical information, including demographics, comorbidity profile, surgery details, GIST-related characteristics, imatinib treatment

[1] FDA approval date in adjuvant setting

characteristics, disease recurrence, and mortality for patients selected for this study.

Outcome Measures

Patient and Physician Characteristics

Patients' characteristics were observed prior to/on the surgery date. Patient' demographics (age, gender), comorbidity profile, GIST-related characteristics (mitotic count, tumor size, location, rupture during surgery, mutation analyses), and imatinib treatment characteristics (average dose prescribed, treatment duration, reason for the choice of treatment) were collected. The pre-treatment Fletcher risk score categories and the Miettinen risk score, indicating the risk of progression, were also computed respectively for patients with complete mitotic information and for patients with gastric and small intestinal GISTs [5, 13, 14].

Data on physicians' characteristics (practice setting, practice size and specialty, region), perceptions, and prescribing patterns were also collected.

Clinical Outcomes: Disease Recurrence and Mortality

The risk of recurrence was compared between patients receiving short-term versus long-term adjuvant imatinib. Disease recurrence was defined as the reappearance of GIST at the same location or as a new GIST lesion and measured during the period spanning from surgery date until the first disease recurrence, death of the patient, or the last date on which the physician had complete patient information, whichever occurred first.

Mortality rates were compared among patients receiving short-term versus long-term imatinib adjuvant therapy and measured during the period spanning from the surgery date until the date of death, or the last date on which the physician had complete patient information, whichever occurred first.

Statistical Analyses

Patient and Physician Characteristics

Patient characteristics and physician practice related differences were compared between patients in the short-term and long-term group using Wilcoxon rank–sum tests for continuous variables and Chi-square tests for categorical variables.

Clinical Outcomes: Disease Recurrence and Mortality Rates

The proportion of patients who had at least one disease recurrence and who died over the study period was reported. In addition, to account for varying observation period durations, separate multivariate Cox proportional-hazards models were used to compare mortality and disease recurrence risks between patients in the long-term and short-term groups while controlling for differences in age, gender, GIST size, GIST location, and mitotic count. Results were reported as hazards ratios with their 95 % confidence intervals and *p* values.

All statistical analyses were carried out with SAS 9.3 statistical software (SAS Institute, Inc., Cary, NC, USA).

Results

Over the 2-month collection period, a total of 318 specialists provided information from patient charts. Over a total of 7,221 eligible patients (short-term, 4,045 versus long-term, 3,176) information was collected from 812 eligible patients receiving adjuvant imatinib (short-term, 406 versus long-term, 406) (Fig. 1). The median duration of the observation period was 970 and 916 for long-term and short-term patients, respectively.

Patient and Physician Characteristics

Demographics and Comorbidity Profile

Most patients were Caucasians (short-term, 71 %, long-term, 75 %, $p=0.236$), from the north east (short-term, 31 %, long-term, 35 %, $p=0.203$) and south regions of the US (short-term, 34 %, long-term, 29 %, $p=0.199$). While patients were similar in age (approximately 59 years old, $p=0.113$), the short-term group included fewer males (59 % versus 70 %, $p=0.002$) (Table 1). The comorbidity profile was generally well balanced between the two groups. The ten most prevalent comorbidities were presented. However, the short-term group had a statistically significant higher prevalence of cardiovascular (11 % versus 6 %, $p=0.004$) and ischemic heart disease (4 % versus 2 %, $p=0.020$) (Table 1).

GIST-Related Characteristics

The average tumor size before resection was significantly lower in the short-term group (6.9 cm versus 8.1 cm, $p<0.001$), and the short-term group had a significantly higher proportion of patients with a low mitotic count (17.5 % versus 9.6 % $p=0.001$) (Table 2). Differences were also observed in GIST locations; more patients in the long-term group had a GIST located in the stomach (54 % versus 46 %, $p=0.035$), and fewer had a GIST located in the pelvis (0.7 % versus 3.7 %, $p=0.004$) (Table 2). Patients in the long-term group had a higher Miettinen risk score (0.40

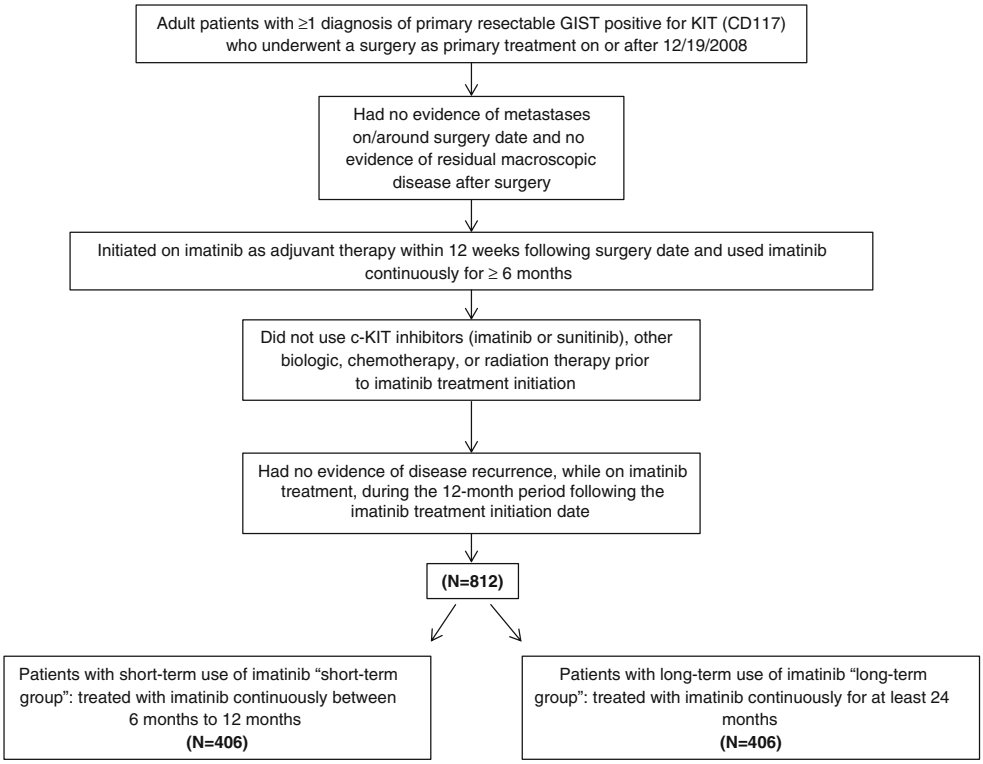

Fig. 1 Sample selection

versus 0.32, p=0.004). Similarly, a higher proportion of patients in the long-term group had a high risk Fletcher score (49 % versus 40 %, p=0.013).

For approximately half of the patients, no mutation test analyses were performed (Table 2). The main reasons stated by physicians for not performing KIT mutation tests were that

Table 1 Comparison of patient characteristics between patients with short-term versus long-term imatinib use

	Patients with long-term imatinib use, n=406	Patients with short-term imatinib use n=406	P value
Demographics			
Age at index date, mean± SD	58.06±9.43	59.16±9.82	0.113
Male, n (%)	282 (69.5)	240 (59.1)	0.002[a]
Ethnicity/race, n (%)			
Caucasian	304 (74.9)	289 (71.2)	0.236
Hispanic	34 (8.4)	41 (10.1)	0.396
Black	38 (9.4)	50 (12.3)	0.176
Asian	27 (6.7)	22 (5.4)	0.461
Native American	2 (0.5)	4 (1.0)	0.412
Other	1 (0.2)	0 (0.0)	-
Comorbid conditions, n (%)			
Hypertension	155 (38.2)	152 (37.4)	0.828
Hyperlipidemia	98 (24.1)	97 (23.9)	0.935
Diabetes	59 (14.5)	79 (19.5)	0.062
Anemia	60 (14.8)	73 (18.0)	0.218
Cardiovascular	23 (5.7)	46 (11.3)	0.004 [a]
Ischemic heart disease	6 (1.5)	17 (4.2)	0.020 [a]
Renal failure	5 (1.2)	11 (2.7)	0.130
Other	3 (0.7)	8 (2.0)	0.129
Other heart disease	5 (1.2)	2 (0.5)	0.255
Cancer other than GIST	5 (1.2)	2 (0.5)	0.255

[a]Significant at the 5 % level

Table 2 Comparison of GIST-related information between patients with short-term versus long-term imatinib use

	Patients with long-term imatinib use, n=406	Patients with short-term imatinib use, n=406	P value
Mitotic rate, n (%)			
<5/50 HPF	39 (9.6)	71 (17.5)	0.001[a]
5/50 HPF	129 (31.8)	128 (31.5)	0.940
6–10/50 HPF	137 (33.7)	123 (30.3)	0.292
>10/50 HPF	69 (17.0)	56 (13.8)	0.206
Unknown	32 (7.9)	28 (6.9)	0.592
Tumor size, n (%)	8.10±6.88	6.89±6.29	<0.001 [a]
<2 cm	2 (0.5)	12 (3.0)	0.007 [a]
2–5 cm	113 (27.8)	167 (41.1)	<0.001 [a]
6–10 cm	227 (55.9)	187 (46.1)	0.005 [a]
>10 cm	64 (15.8)	40 (9.9)	0.012 [a]
Miettinen risk, mean±SD	0.39±0.32	0.32±0.33	0.004 [a]
Fletcher risk categories, n (%)			
Very low risk	1 (0.2)	4 (1.0)	0.178
Low risk	55 (13.5)	102 (25.1)	<0.001 [a]
Intermediate risk	111 (27.3)	101 (24.9)	0.424
High risk	197 (48.5)	162 (39.9)	0.013 [a]
Unknown	42 (10.3)	37 (9.1)	0.554
GIST location, n (%)			
Stomach	218 (53.7)	188 (46.3)	0.035 [a]
Small intestine	121 (29.8)	118 (29.1)	0.817
Colon	26 (6.4)	34 (8.4)	0.283
Rectum	5 (1.2)	9 (2.2)	0.281
Pelvis	3 (0.7)	15 (3.7)	0.004 [a]
Number of patients with no mutation analyses performed, n (%)	199 (49.0)	209 (51.5)	0.483
Reasons why KIT mutation tests were not performed, n (%)			
Not a standard of care/no indications to do it	70 (34.8)	75 (35.7)	0.683
Would not have change therapy/management or the physician was not aware of how the results should have impact GIST management decision	69 (34.7)	57 (27.3)	0.106
Pathology issues (i.e., pathologist elsewhere or patient had surgery elsewhere and could not get tissue, mishandled by pathology department, or not enough tissue)	7 (3.5)	8 (3.8)	0.868
Cost/no insurance/ patient decision	9 (4.5)	19 (9.1)	0.068
Already tested (results not available)	5 (2.5)	7 (3.3)	0.617
C-KIT was positive, therefore no further testing	13 (6.5)	5 (2.4)	0.042 [a]
Not ordered by surgeon	0 (0.0)	8 (3.8)	–
Don't know	1 (0.5)	1 (0.5)	0.972
Testing was not available	27 (13.6)	30 (14.4)	0.819

The five most frequent GIST locations in the short-term group are reported. Other GIST locations included omentum (short-term 2.7 %, long-term 1.2 %), retroperitoneum (short-term 2.5 %, long-term 2.7 %), gastroesophageal junction (short-term 2.2 %, long-term 1.2 %), appendix (short-term 1.5 %, long-term 2.0 %), esophagus (short-term 1.2 %, long-term 0.5 %), pancreas (short-term 0.2 %, long-term 0.2 %), and liver (short-term 0.0 %, long-term 0.2 %), and differences were not statistically significantly different between the two groups

[a] Significant at the 5 % level

(1) these tests were not a standard of care, and/or there was no indication to do it (long-term, 35 %, short-term, 36 %, p=0.683) and (2) patient management course would not change based on results/physicians were not aware of the impact on therapy management (long-term, 35 %, short-term, 27 %, p=0.106).

Treatment Characteristics

On average, patients in the short-term and long-term groups were treated with imatinib for approximately 10 and 27 months, respectively (Table 3). Patients were generally

Table 3 Comparison of imatinib treatment characteristics between patients with short-term versus long-term imatinib use

	Patients with long-term imatinib use, n=406	Patients with short-term imatinib use, n=406	P value
Duration of imatinib treatment (in months), mean±SD	26.73±10.43	10.36±2.15	<0.001[a]
Average initial dose of imatinib			
Dose <400 mg, n (%)	7 (1.7)	5 (1.2)	0.561
Dose=400 mg, n (%)	387 (95.3)	384 (94.6)	0.631
Dose >400 mg, n (%)	12 (3.0)	17 (4.2)	0.344
Reason for the choice of imatinib as adjuvant therapy, n (%)			
Per treatment guidelines	300 (73.9)	285 (70.2)	0.241
Patient was at increased risk of recurrence	207 (51.0)	184 (45.3)	0.106
Evidence of residual microscopic disease	8 (2.0)	17 (4.2)	0.067
Results of KIT mutation tests	57 (14.0)	53 (13.1)	0.682
The physician treats all patients with imatinib	90 (22.2)	98 (24.1)	0.506
Other	5 (1.2)	4 (1.0)	0.737

[a] Significant at the 5 % level

initiated on imatinib 400 mg (95 % in both groups, p=0.631) as recommended in guidelines, and most patients were still treated with imatinib on the same dose over the observation period; few patients had an imatinib dose increase (short-term, 0.7 % versus long-term, 1.0 %, p=0.716) or decrease (short-term, 4.7 % versus long-term, 3.0 %, p=0.187) or switched to sunitinib (short-term, 2.7 % versus long-term, 0.7 %, p=0.037) (results not presented).

Reasons reported by physicians for treating patients with adjuvant imatinib were similar across the two groups (Table 2). The two main reasons reported were: per treatment guidelines (long-term, 74 %, short-term, 70 %, p=0.241) and the risk of recurrence (long-term, 51 %, short-term, 45 %, p=0.106).

Characteristics of Surveyed Physicians and Perception of Outcomes

Among the 318 surveyed physicians, most were medical oncologists (47 %) or hematologists/oncologists (51 %), working in a private practice setting (78 %) of small or intermediate size (54 %) (i.e., two to nine oncologists) (results not presented).

Overall, 86 % of the physicians believed that long-term imatinib treatment reduced the risk of disease recurrence; these physicians reported that 52 % of their patients received long-term imatinib therapy whereas 48 % received short-term therapy. In contrast, among physicians who did not believe in the benefits of long-term imatinib treatment, a greater proportion of their patients were treated with short-term therapy (59 % versus 41 %). Although patient's risk profile was the main factor considered in a physician's decisions to prescribe long-term imatinib adjuvant therapy (78 % of physicians), drug tolerability (72 %), age (younger) (61 %), safety profile (39 %), treatment response (28 %), and financial reasons (27 %) were also other important considerations for treatment duration related decisions (results not presented).

Clinical Outcomes

Risk of Disease Recurrence

Over the observation period, compared with long-term patients, significantly more patients in the short-term group had at least one disease recurrence (5.9 % versus 1.2 %, p<0.001) (Table 4). Among patients who had a disease recurrence, the median time between surgery and the first disease recurrence was 730 and 717 days for short-term and long-term patients, respectively (results not presented). After controlling for confounders, the adjusted risk of recurrence was 5.30 times (95 % CI, 2.00–14.07, p<0.001) higher in the short-term group (Table 4).

Mortality Risk

The use of imatinib over a longer time period was also associated with a reduction in mortality (Table 4). Compared with patients in the long-term group, significantly more patients in the short-term group died during the observation period (7.1 % versus 2.0 %, p<0.001) (Table 4). After controlling for confounding factors, the adjusted mortality rate was 4.02 times (95 % CI, 1.82–8.90, p<0.001) higher in the short-term group.

Discussion

Tumor resection with clear margins is the mainstay of treatment for localized primary resectable GIST [12]. However,

Table 4 Comparison of rates of disease recurrence and mortality between patients with short-term versus long-term imatinib use

	Proportion of patients with the event, *n* (%)		Unadjusted hazard ratio	*P* value	Adjusted hazard ratio	*P* value	*P* value
	Long-term patients	Short-term patients					
Disease recurrence	5 (1.2)	24 (5.9)	<0.001[a]	5.49 (2.09–14.40)	<0.001 [a]	5.30 (2.00–14.07)	<0.001 [a]
Mortality	8 (2.0)	29 (7.1)	<0.001 [a]	4.19 (1.91–9.19)	<0.001 [a]	4.02 (1.82–8.90)	<0.001 [a]

[a] Significant at the 5 % level

studies showed that one out of two patients generally relapse at some point after curative surgery [9]. This study showed that, compared with long-term patients, the risk of recurrence was 5.30 times higher and mortality risk was 4.02 times higher in patients with short-term adjuvant imatinib use, suggesting that patients with primary resectable GIST would benefit from long-term treatment with adjuvant imatinib. These findings are consistent with results from a recent multicenter, prospective, randomized Phase III study which showed superior RFS (65.6 % versus 47.9 %) and overall survival (92.0 % versus 81.7 %) at 5 years among patients receiving longer adjuvant imatinib treatment (3 versus 1 year) [11, 15, 16]. According to the 2012 NCCN Guidelines, postoperative use in of imatinib for at least 36 months should be considered in high-risk patients [12]. Though benefits of long-term treatment are clearly illustrated in the published literature as well as in our study, in practice, the key debate around factors to be considered by physicians to appropriately select patients for long-term adjuvant imatinib treatment remains unresolved.

The published literature suggests that all factors including tumor size, location, mitotic count, and tumor rupture during surgery should be considered while determining patients' risk of recurrence. However, results from our study showed that, among these, only tumor size and mitotic count seemed to play an important role in the treatment duration decision. In addition, although tumor rupture during surgery or a GIST location outside of the stomach have been associated with higher risk of recurrence, no significant differences were observed in our study [17]. Tumor rupture occurred rarely, which may account for our observation (see Table 2). The choice between long-term and short-term imatinib therapy was primarily dependent on the assessment of patients' pre-treatment risk of recurrence. Physicians' perception of the effectiveness of long-term imatinib treatment in reducing the risk of recurrence also played an important role; patients who received long-term imatinib seemed to have a higher pre-treatment risk profile compared with patients on short-term imatinib treatment. Although the proportion of patients with a high-risk profile (based on Fletcher classification) was higher in the long-term imatinib group, the proportion was also high in the short-term group (39.9 %), suggesting that a sizeable proportion of high-risk patients who should be treated for longer duration were receiving short-term imatinib treatment.

Although there is no consensus on the role of mutational testing as a prognostic factor, especially in non-metastatic patients, studies have shown a high association between the presence of KIT mutations and treatment response to tyrosine kinase inhibitors [18]. The role of mutational testing in determining imatinib treatment duration and dose for advanced/metastatic disease has been recognized in the literature. Recent studies have also shown that mutational status can be considered as a prognostic factor in patients with localized GIST treated with adjuvant imatinib [18–20]. However, to date, there are no clear recommendations regarding the need to perform systematic KIT mutational testing in non-metastatic primary GIST patients. According to the NCCN Task Force Report, mutation analysis is not "routinely recommended" at diagnosis [1]. However, the NCCN report also indicates that the mutational analysis may be useful in selecting patients for postoperative therapy after complete resection of primary GIST, by identifying patients at higher risk for recurrence [1]. However, in our study, KIT mutation status was known in only 50 % of patients in both treatment groups. The two main reasons indicated by physicians for not performing KIT mutation tests were that (1) they were not considered standard of care and that the results would not have changed treatment decision and (2) the physician was not aware of how the results should impact treatment decisions. The relatively high percentage of patients with a high risk profile in the short-term group and the relatively low percentage of patients for whom the mutational testing was performed suggest a lack of consensus about risk assessment methods and the importance of considering mutational testing in GIST patients using imatinib adjuvant treatment.

To the best of our knowledge, this is the first study to compare the risk of recurrence and mortality in GIST patients treated with short-term versus long-term adjuvant imatinib therapy in a non-trial setting and to collect information about physicians' perceptions of risk in treatment decisions. Findings from this study provide information on the benefits of long-term imatinib use and a more complete picture of the characteristics of GIST patients treated with imatinib over a shorter versus longer period of time and prescribing decision drivers among physicians in a non-trial setting.

The present study is subject to common limitations that are inherent to retrospective studies using patient chart surveys. First, the generalizability of these findings may be limited if patients treated by physicians who participated in the survey had systematically different characteristics from patients treated by physicians who did not. However, in order to ensure a representative sample, every effort was made to recruit physicians and to collect information on randomly selected patients. Second, an inherent limitation of the patient selection is that patients in the long-term group had to survive for at least 24 months while patients in the short-term group survived for a minimum of 6 months. To minimize this potential bias, short-term patients were selected only if imatinib was discontinued for a reason other than death. In addition, patients in the long-term group were excluded only if they had a recurrence during the first 12 months of treatment. Therefore, some patients may have had a recurrence between 12 and 24 months after imatinib initiation, that is, before they can benefit from the long-term imatinib use. Third, the impact of imatinib treatment duration on the risk of recurrence and mortality might vary depending on patients' risk profile. Although we did control for patients' pre-treatment risk profile in multivariate regression analyses, due to the relatively small sample size and small number of events, results were not stratified by risk profile. Further research would be warranted to analyze the impact of imatinib treatment duration on disease recurrence and mortality for specific risk profile subgroups.

Conclusion

Results from our study showed that, despite the higher risk profile of long-term imatinib patients, the use of imatinib over a longer period of time was associated with a reduction in long-term risk of disease recurrence and mortality. The patient's pre-treatment risk profile and physicians' perception of the effectiveness of long-term imatinib treatment were the main factors that drove the decision to treat a patient with imatinib over a shorter versus a longer period of time, although a relatively high proportion of patients in the short-term group had a high-risk profile. The significant percentage of patients with a high-risk profile in the imatinib short-term treatment group and the low percentage of patients for whom mutational testing was performed suggest that more education is needed to better inform physicians about risk assessment and the importance of considering mutational testing in GIST patients using imatinib adjuvant treatment.

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Ethical Standards Data used in this study were de-identified, and thus institutional review board approval was not required. Institutional review board exemption was obtained.

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