

Non-Standard Dosing In Gastrointestinal Stromal Tumors: A reGISTry Observation

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UPDATED ABSTRACT

Background: Imatinib has been studied in over 2,500 patients in phase II and III trials in both the adjuvant and metastatic settings. Standardized dosing using 400 and 800 mg has proven to be efficacious. Careful dose escalation from 400 mg/d to 800 mg/d is hypothesized to improve the tolerability of the higher dose.

Methods: We used a data collection tool designed to provide insights into practice patterns surrounding the diagnosis and management of GIST pts (reGISTry) to explore non-clinical trial dosing as initial dose or dose modification in community and academic practices.

Results: Since November 2004, 1053 patients have been enrolled. Out of 613 pts receiving imatinib, non-standard dosing was observed in 5%, 12.5% and 20.7% of patients receiving imatinib in the neoadjuvant, adjuvant and metastatic settings. Primary reasons for non-standard dose changes were disease progression and toxicity. In patients with reported Exon 9 mutations, the median imatinib dose administered was 400 mg. Notable variations in non-standard dosing were reported in both the adjuvant and metastatic/unresectable settings as illustrated in the table.

Examples of Non-Standard Dosing in reGISTry

Dose (mg)	Schedule
50, 100, 150, 200, 250, 275, 300, 350, 500, or 700	QD
100	BID or TID
200, 300 or 400	Two days on / one day off
200 or 400	QOD
200/300; 200/400	Alternating daily
300/200/0 or 300/300/0	Repeating cycle
400	Three times weekly, M-F, or 4 times weekly
400/800	400 M – F; 800 S, S

Conclusions: Despite the demonstrated benefit of standardized doses, non-standard dosing schemas were observed. Dosing as observed in the reGISTry may lead to suboptimal trough levels due to the pharmacokinetic profile of imatinib. Further education in the importance of dose intensity and side effect management may potentially improve clinical outcomes.

INTRODUCTION

- Annual incidence of GIST in US is 4,500-6,000 patients.
- The treatment of GIST is evolving as new therapies are introduced and additional data are collected on optimal treatment strategies.
- Most data on treatment of GIST patients were derived from clinical studies, reflecting practice at mainly academic referral centers. The reGISTry, an observational, secure, Internet-based portal database, was designed to characterize evolving patterns of care for patients with GIST in both community and academic practice settings.

OBJECTIVES

- To describe treatment and dosing patterns in patients with GIST treated with imatinib, overall and by patient and provider characteristics.
 - This analysis explored imatinib dosing patterns in patients being managed in community and academic practices.
- To provide individual physicians with information regarding management of patients with GIST as well as aggregate experience of all physicians participating in the registry.

METHODS

- Enrolling Sites
 - More than 200 sites are expected to participate, with 122 sites currently active, and will be stratified by institution type: community based or academic center.
- Size / Duration
 - Expect 1800 patients to participate and will be followed for up to seven years.
 - Enrollment started in November 2004 and is ongoing.
- Data Collection
 - Documentation of care – no specified patient visits or interventions.
 - The study uses Electronic Data Capture (EDC) system. For more information concerning the study, please visit the reGISTry Website at www.gistregistry.net.

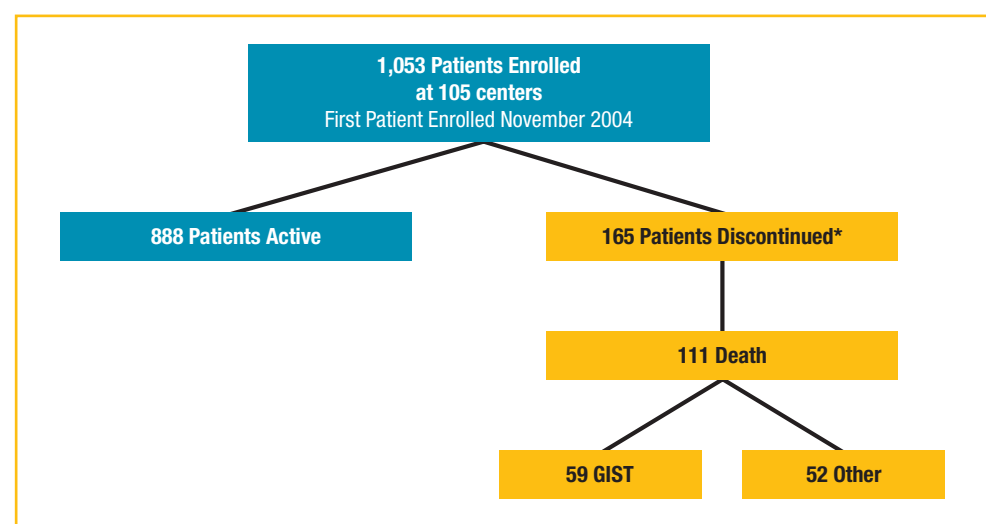
- Statistical Analysis
 - Data analysis will be performed approximately every 6 months using descriptive statistics and summarizing changes over time.

Patient Data Being Collected

- Demographics
 - Date of birth, gender, ethnicity
- Diagnostic History
 - Date of GIST diagnosis, presenting signs, symptoms
 - Diagnostic tests performed and results
 - Imaging tests, lab tests, pathology, CD117 testing and special tests
 - Location, size, mitotic count of primary lesion
 - Location of metastatic lesions
 - Results of mutational analysis
 - Family history
- Treatment History
 - First treatment:
 - Surgery, chemotherapy, targeted therapy, radiation, supportive care
 - Drugs, doses, duration, neoadjuvant/adjuvant treatment
 - Subsequent courses of therapy
 - Reason for change, dates of change
 - Criteria for evaluating response
 - Radiographic tests performed, results
- Disease Management and Treatment History
 - Specialty of treating physician
 - Treatment history
 - Changes in patient status
 - Type of therapy received for progression, location of new lesions
 - Date, primary cause of death
 - Medical resource use
- Safety
 - Serious Adverse Events related to Novartis products that led to change in GIST therapy

RESULTS

Figure 1. Patient Status



*Other reasons for discontinuation include: patient transferred; administration problems; patient lost to follow-up.

Table 1. Patient Demographics

Institution Type Number of Patients	All Sites = 105 N=1,053 (100%)	Community Practices = 84 N=619 (59%)	Academic Institutions = 21 N=434 (41%)
Gender			
Male (%)	528 (50)	310 (50)	218 (50)
Female (%)	525 (50)	309 (50)	216 (50)
Median Age (years)	63 (15–92)	65 (17–92)	60 (15–92)
Race			
Caucasian	794 (75%)	473 (76%)	321 (74%)
African American	174 (17%)	95 (16%)	78 (18%)
Asian	28 (3%)	13 (2%)	15 (3%)
Hispanic	32 (3%)	19 (3%)	13 (3%)
Other/Unknown	25 (2%)	18 (3%)	7 (2%)
Referrals			
Treated where diagnosed	664 (63%)	383 (62%)	281 (65%)
Referred to tertiary care	389 (37%)	236 (38%)	153 (35%)

- As of the data cut-off date of September 17, 2009, 1053 patients with GIST have been enrolled into the reGISTry (Figure 1).
- In total, 613 enrolled patients (58.2%) received imatinib therapy.
 - The median daily imatinib dose for all patients was 400 mg (132 – 938.4 mg/day).
 - Non-standard dosing (eg, doses other than 400 mg, 600 mg or 800 mg daily) was explored by treatment intent (eg, neoadjuvant, adjuvant and metastatic disease) and treatment setting (eg, community practice and academic centers).

Imatinib Dosing: Neoadjuvant Treatment

- The majority of patients (80.0%) received imatinib 400 mg daily as their initial dose (Table 2).
- Three patients (5%) received non-standard imatinib dosing in the neoadjuvant setting (Table 3).
- The mean duration of imatinib therapy in the neoadjuvant setting was 144 and 215 days in patients treated in academic and community settings, respectively ($P = 0.19$).

Table 2. Initial Imatinib Dose By Treatment Intent

	100 mg	150 mg	200 mg	300 mg	400 mg	600 mg	800 mg
Neoadjuvant (n = 60)	0	0	2 (3.3%)	1 (1.7%)	48 (80%)	9 (15%)	0
Adjuvant (n = 208)	2 (<1%)	0	6 (2.9%)	2 (<1%)	181 (87.0%)	12 (5.7%)	5 (2.4%)
Metastatic Disease (n = 401)	3 (<1%)	1 (<1%)	16 (4.0%)	5 (1.2%)	312 (77.8%)	35 (8.7%)	29 (7.2%)

*Note: patients could have received imatinib in multiple treatment settings.

Table 3. Non-Standard Dosing By Treatment Intent and Setting

	Non-Standard Dosing, N (%)	Academic Center, N	Community-Based Practice, N
Neoadjuvant (n = 60)	3 (5%)	1	2
Adjuvant (n = 208)	26 (12.5%)	10	16
Metastatic Disease (n = 401)	83 (20.7%)	32	51

Imatinib Dosing: Adjuvant Treatment

- The majority of patients (87.0%) received imatinib 400 mg daily as their initial dose for adjuvant therapy (Table 2).
- Twenty-six patients (12.5%) received non-standard imatinib dosing in the adjuvant setting (Table 3).
 - The most common non-standard dose in the adjuvant setting was 300 mg daily (27.8% of non-standard doses)
 - Imatinib dosing was escalated or reduced with similar frequencies (47.1% and 52.9%, respectively).
 - One patient (1%) in the adjuvant setting escalated the imatinib dose upon progression.
 - The mean (median) number of days between dose adjustment for each patient was 227 days with no discernable difference between academic and community settings (226 and 229 days, respectively).
 - 17 patients (8.2%) receiving adjuvant imatinib switched to sunitinib; of those 6 switched due to disease progression.

- The most common reasons for dose adjustment were adjuvant care (care being dictated based on current standard of 1 year of adjuvant therapy; 67.8%), disease progression or recurrent disease (17.3%), unacceptable toxicity (15.4%) and clinical trial (14.4%).
- As was observed with neoadjuvant and metastatic disease, non-standard imatinib dosing was observed more frequently in community-based practices than in academic centers (Table 3).
- The mean duration of imatinib therapy administered in the adjuvant setting was 407 days in academic centers and 566 days in community practices ($P = 0.01$).

Imatinib Dosing: Metastatic Treatment

- The majority of patients (77.8%) received imatinib 400 mg daily as their initial dose for metastatic disease (Table 2).
- Eighty-three patients (20.7%) received non-standard imatinib dosing in the metastatic setting (Table 3).
 - Of these 83 patients, 61 (73.5%) had initially received imatinib 400 mg daily.
 - In total, 102 patients (25.4%) with metastatic disease switched from imatinib to sunitinib; of those 54 did so after progression on imatinib.
- The most common non-standard dose in the metastatic setting was 200 mg daily (29.4% of non-standard doses).
- Increasingly complicated dosing schemas were used in patients with metastatic disease (Table 4).

Table 4. Examples of Non-standard Imatinib Dosing Schemas

Dose (mg)	Schedule
50, 100, 150, 200, 250, 275, 300, 350, 500, or 700	QD
100	BID or TID
200, 300 or 400	Two days on / one day off
200 or 400	QOD
200/300; 200/400	Alternating daily
300/200/0 or 300/300/0	Repeating cycle
400	Three times weekly, M-F, or 4 times weekly
400/800	400 M – F; 800 S, S

BID: twice daily; M-F: Monday – Friday; QD: once daily; QOD: every other day; S,S: Saturday, Sunday; TID: three times daily.

Imatinib Dosing by Tumor Size, Mitotic Count or Exon 9 Mutation

- Most patients received imatinib 400 mg daily regardless of tumor size or mitotic count.
 - A small percentage of patients with high-risk GIST tumors (large tumor size, >5 mitoses/50 high powered field [HPF]) received imatinib doses greater than 400 mg/day (Table 5).
- The tumor size and mitotic count were unknown in 81 (17.9%) and 213 (27.1%) patients, respectively.

Table 5. Maximum Imatinib Dose By Tumor Size And Mitotic Count

	200 mg	300 mg	400 mg	600 mg	800 mg
Tumor Size (cm), %					
>10 (n = 165)	1.2%	1.8%	72.1%	6.7%	18.2%
6–10 (n = 110)	3.6%	0.9%	73.6%	5.5%	16.4%
2–5 (n = 80)	1.2%	0%	78.8%	12.5%	7.5%
<2 (n = 16)	0%	0%	75.0%	12.5%	12.5%
Unknown (n = 81)	1.2%	1.2%	55.6%	22.2%	19.8%
Mitotic Count (HPF), %					
>10/50 (n = 79)	5.1%	0%	74.7%	2.5%	17.7%
6–10/50 (n = 48)	0%	6.2%	75.0%	6.2%	12.5%
≤5/50 (n = 112)	0.9%	0.9%	80.4%	8.9%	8.9%
Unknown (n = 213)*	1.4%	0.5%	63.4%	15.0%	19.7%

*An alternative approach could have been utilized to assess mitotic count.

- KIT exon 9 mutation status was assessed in 15 patients (1.4% of 1053 patients). Eleven patients (73.3% of the population tested) had a documented KIT exon 9 mutation (Table 6); exon 9 mutations were documented more commonly in academic centers versus community-based practices (81.8% vs 18.2%).
 - The median daily imatinib dose in patients with KIT exon 9 mutations was 400 mg (200 – 451.6 mg).
 - One patient (9.1%) received imatinib 800 mg daily.

Table 6. Imatinib Dosing In Patients With KIT Exon 9 Mutations

	Treatment Intent	Imatinib Daily Dose, mg
Community Practice	Adjuvant (n = 1) Metastatic Disease (n = 1)	200 (n = 1) 400 mg escalated to 800 mg (n = 1)
Academic Center	Adjuvant (n = 3) Neoadjuvant* (n = 2) Metastatic disease (n = 4) [†]	400 (n = 3) 400 mg (n = 2) 400 mg (n = 2) 400 mg escalated to 800 mg (n = 1) 300 mg escalated to 800 mg (n = 1)

*One patient progressed to metastatic disease.

[†]Three patients received highly variable treatment schedules in the metastatic setting.

CONCLUSIONS

- reGISTry provides a means to evaluate patient care trends in GIST over time in academic centers and community-based practices.
- The reGISTry dosing analyses suggests that the majority of patients are receiving the indicated dose of imatinib 400 mg daily.
- Non-standard dosing was observed more frequently in community-based practices than in academic centers and in patients with metastatic disease.
 - Numerous dosing frequencies, some involving complicated dosing schemas, mimicking sunitinib dosing strategies were employed for imatinib. The impact of these variations in imatinib therapy on patient outcomes is not known.
 - A notable number of patients received less than imatinib 400 mg/day which may result in suboptimal trough levels. Maintaining optimal imatinib dosing may improve long-term clinical outcomes; imatinib trough concentrations <1,100 ng/mL Cmin are associated with a shorter time to progression and lower rate of clinical benefit.¹
- Non-standard imatinib dosing due to unacceptable toxicity occurred in ~15% of patients, imatinib dose intensity should be maintained through proper management of adverse events.²
- Although imatinib 800 mg/day is recommended in patients with KIT exon 9 mutation and in patients who have progressed³, few patients in reGISTry received doses greater than 400 mg/day.
- Tumor location, tumor size and mitotic count have been shown to have predictive value⁴ and should be documented in all patients to estimate the risk of relapse⁵; however, the tumor size and mitotic rate was unknown for many patients in the reGISTry.
- Iterative data analyses over the next 2 years will allow for comparison of management patterns as advances in the understanding of GIST evolve.
- Education regarding side effect management may help maintain imatinib dose intensity which may potentially improve clinical outcomes in patients with GIST.

References

- Demetri GD, Wang Y, Wehrle E, et al. Imatinib plasma levels are correlated with clinical benefit in patients with unresectable/metastatic gastrointestinal stromal tumors. *J Clin Oncol.* 2009;27:3141-3147.
- Casali PG, Lost L, Reichardt P, et al. Gastrointestinal stromal tumours: ESMO Clinical Recommendations for diagnosis, treatment and follow-up. *Ann Oncol.* 2009;20:iv64-iv67.
- National Comprehensive Cancer Network.NCCN Clinical Practice Guidelines in Oncology soft tissue sarcoma v.2.2009.
- DeMatteo RP, Gold JS, Saran L, et al. Tumor mitotic rate, size, and location independently predict recurrence after resection of primary gastrointestinal stromal tumor (GIST). *Cancer.* 2008;112:608-615.