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Long-term results of adjuvant imatinib mesylate in localized, high-risk, primary gastrointestinal stromal tumor (GIST): ACOSOG Z9000 (Alliance) intergroup phase 2 trial

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Abstract

Objective—To conduct the first adjuvant trial of imatinib mesylate for treatment of gastrointestinal stromal tumor (GIST).

Summary Background Data—GIST is the most common sarcoma. While surgical resection has been the mainstay of therapy for localized, primary GIST, postoperative tumor recurrence is common. The *KIT* proto-oncogene or, less frequently, platelet-derived growth factor receptor alpha (*PDGFRA*) is mutated in GIST; the gene products of both are inhibited by imatinib mesylate.

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CONFLICT OF INTEREST: Drs. DeMatteo, Corless, von Mehren Maki, Pisters, and Demetri report receiving honoraria from Novartis and have served on Novartis advisory boards. No other relevant conflicts of interest were reported.

Preliminary data were presented at the 2005 meeting of the American Society of Clinical Oncology (ASCO) and the 2007 meeting of the Gastrointestinal Cancers Symposium of ASCO.

Methods—This was a phase II, intergroup trial led by the American College of Surgeons Oncology Group (ACOSOG), registered at [ClinicalTrials.gov](https://clinicaltrials.gov) as NCT00025246. From 09/2001 to 09/2003, we accrued 106 patients who had undergone complete gross tumor removal but were deemed at high risk for recurrence. Patients were prescribed imatinib 400 mg/day for 1 year and followed with serial radiologic evaluation. The primary endpoint was overall survival (OS).

Results—After a median follow-up of 7.7 years, the 1-, 3-, and 5-year OS rate was 99, 97, and 83%, which compared favorably with a historical 5 year OS rate of 35%. The 1-, 3-, and 5-year RFS rate was 96, 60, and 40%. On univariable analysis, age and mitotic rate were associated with OS. On multivariable analysis, the RFS rate was lower with increasing tumor size, small bowel site, *KIT* exon 9 mutation, high mitotic rate, and older age.

Conclusion—Adjuvant imatinib in patients with primary GIST who are at high risk of recurrence prolongs OS compared to that of historical controls. Optimal duration of adjuvant therapy remains undefined. (NCT00025246)

INTRODUCTION

It has now been established that of the over 50 subtypes of sarcoma, gastrointestinal stromal tumor (GIST) is the most common.[1] The annual U.S. incidence is approximately 4,000. GIST originates most frequently in the stomach and small intestine, occasionally in the rectum and esophagus, and rarely in the colon or extra-intestinal sites within the abdomen. [2] Surgery has been the standard of care for localized (i.e., without metastasis), primary GIST. Historically, despite complete gross tumor resection, as many as 50% of patients eventually died from recurrent disease.[3] Tumor recurrence typically involves the liver or peritoneum. Before the year 2000, there were no effective systemic agents for GIST.[4]

In the last 15 years, it was discovered that approximately 85% of GISTs harbor an activating mutation in either the *KIT* proto-oncogene (85%) or platelet-derived growth factor receptor alpha (*PDGFRA*) (3-5%).[5, 6] Imatinib mesylate (Gleevec®, Novartis Pharmaceuticals, Basel, Switzerland) is a selective inhibitor of KIT and PDGFRA (as well as ABL/BCR-ABL, DDR, and CSF1R) and has become the first line agent for advanced GIST. In patients with metastatic GIST, imatinib has increased the median survival from 9 months to over 4 years.[7-11] After the initial results of the B2222 trial for advanced GIST were shared at a National Cancer Institute meeting in December 1999, we designed the American College of Surgeons Oncology Group (ACOSOG) Z9000 trial to assess the efficacy of imatinib in the adjuvant setting for patients at high risk of tumor recurrence. Given that imatinib was effective for metastatic GIST, we hypothesized that adjuvant imatinib would prolong overall survival following the resection of localized, primary GIST in patients at high risk of postoperative tumor recurrence.

METHODS

Patient Eligibility

Patients were eligible if they had complete gross resection of a localized, primary GIST and were deemed to be at high risk for postoperative tumor recurrence. “High risk” was defined as tumor diameter >10 cm, intraperitoneal tumor rupture, or up to 4 peritoneal implants.

Patients were eligible if at least 16 years old, with an Eastern Cooperative Oncology Group (ECOG)/Zubrod performance status of ≤ 2 . Patients were ineligible if they had within 28 days of registration any detectable tumor by postoperative imaging, which included a baseline chest x ray (or chest CT) and an abdomen and pelvis CT scan with intravenous and oral contrast, or MRI with intravenous contrast. Additional inclusion criteria included adequate renal, hematologic, and hepatic function and, when relevant, a negative serum pregnancy test. Patients were excluded if they had been: treated postoperatively with imatinib, chemotherapy, radiation therapy, or investigational agents; breast feeding; or taking full dose warfarin. Also excluded were patients with an active infection requiring antibiotics within 14 days before registration or New York Heart Association Class 3 or 4 cardiac disease. The study was approved by the institutional review board (IRB) of each participating institution, and written informed consent was obtained from all patients.

Study Design and Conduct

Patients were registered within 70 days following complete gross tumor resection and started therapy within 84 days. Imatinib 400 mg/day was prescribed for 1 year. Patients were seen frequently in the first six months, every 3 months until year 2, and then every 6 months until year 5 with physical examination and laboratory tests (CBC with differential, creatinine, bilirubin, alkaline phosphatase, and aspartate and alanine aminotransferases). CT scans with intravenous and oral contrast (or MRI with intravenous contrast) of the abdomen and pelvis were performed every 3 months for the first 2 years and then every 6 months for the following 3 years. Tumor recurrence was determined by clinical impression or biopsy. Patients with tumor recurrence were eligible to resume imatinib 400 mg/day. Drug tolerability was graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE version 3.0). Attribution was rated as definite, probable, possible, unlikely, or unrelated to the study drug. Dose modifications were made for grade 3 and 4 events (excluding anemia) that were thought to be at least possibly related to treatment. Patients maintained a diary of drug compliance and adverse events. See Figure 1 for CONSORT diagram.

The trial was led by ACOSOG and registered at [ClinicalTrials.gov](https://clinicaltrials.gov) as NCT00025246. It was endorsed by the Southwest Oncology Group (SWOG), Cancer and Leukemia Group B (CALGB), and Eastern Cooperative Oncology Group (ECOG), all of which participated through the Cancer Trials Support Unit (CTSU). The trial was conducted via the Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute and sponsored by Novartis. Novartis employees provided input regarding study design, but did not participate in data collection or analysis. Data collected by local institutions were transferred electronically to the ACOSOG central database.

Pathologic Analysis

The histologic diagnosis of GIST was confirmed by a central sarcoma pathologist (CRA) before patient enrollment. Patients were only eligible if their tumors had appropriate microscopic morphology and expressed KIT protein (CD117) by immunohistochemistry. Retrospectively, the mitotic rate was counted by 2 pathologists (CC and VK) and reported as

the number of mitoses per 50 high power fields (totaling 11.87 mm²). Mutational analysis in tumor from consenting patients was performed as described previously.[12]

Statistical Analysis

The primary endpoint was to compare overall survival (OS) to that of historical controls. OS was defined as the time from patient registration to death from any cause. Based on published data, 5 year OS in high risk GIST patients was estimated to be 35% with surgery alone.[3, 13] Planned accrual was 89 patients. Adjuvant imatinib was to be considered efficacious in this patient population if 40 or more patients out of the first 89 eligible patients enrolled to the trial survived five years or longer from trial registration time. This decision criteria and sample size had a level of significance of 0.033 and 86% power to detect an increase in the 5-year survival rate from 35% to 50%. Secondary endpoints included recurrence-free survival (RFS) and patient safety. RFS was defined as the time from patient registration to tumor recurrence or death from any cause. RFS and OS were estimated using the Kaplan-Meier method. Comparisons of RFS and OS between patient subgroups were performed using the log-rank test; a Cox proportional hazards model was used to estimate the hazard ratio and 95% confidence interval (CI). Multivariable Cox models that adjusted for the high risk factors of tumor size and tumor location were used for exploratory analyses to identify additional variables that might potentially be prognostic. The database was locked on January 24, 2012 for analysis. All analyses were performed using SAS 9.3 (SAS Institute Inc.; Cary, North Carolina).

RESULTS

Patients and Clinicopathologic Features

Between September 2001 and September 2003, 149 patients consented to the protocol. In 13 (8.7%) patients, a diagnosis of GIST could not be confirmed on prospective central pathologic review. Another 27 withdrew or did not meet eligibility criteria. There were a total of 109 patients (Figure 1) enrolled at 48 institutions (17 via the CTSU). Three patients did not have high risk GIST and were excluded from the current analysis.

The patient demographics and tumor features are listed in Table 1. There were more males than females and the median age was 58 years. The median time to start imatinib therapy was 59 days after surgery. The median tumor size was 13 cm. Of the 106 patients, 85% were eligible based on tumor size, while 17% had intra-abdominal tumor rupture before or during surgery and 13% had <4 peritoneal metastases. Most (92%) of the tumors originated from the stomach or small intestine. The rate of positive microscopic surgical margins was 10%, similar to that reported previously.[3] About half of tested patients had a high (>5) mitotic rate. Adequate tissue for mutation analysis was available in 78 patients. A *KIT* exon 11 mutation was detected in 58% of tumors. The frequency of a *KIT* exon 9 mutation was 13%, as was that of a *PDGFRA* mutation. Meanwhile, 12% of tumors were wild-type (i.e., lacking a *KIT* or *PDGFRA* mutation). There were associations between tumor mutation and mitotic rate, and between tumor mutation and tumor location (Table 2). Tumors containing a *KIT* exon 11 more often had a high mitotic rate, while tumors with a *PDGFRA* mutation nearly

always had a low mitotic rate and were located in the stomach. As expected, all tumors with a *KIT* exon 9 mutation originated in the small intestine.[14]

Safety

Overall, 83% of patients completed the prescribed year of therapy with 69% receiving the prescribed dose (Figure 1). Dose reductions were necessary in 15%. Therapy was generally well tolerated, consistent with previous experience in GIST patients receiving imatinib for advanced disease or as an adjuvant.[7, 15] The most common adverse events were edema, fatigue, diarrhea, nausea, and dermatitis (Table 3). Grade 1 and 2 events were common, grade 3 events occurred in 26% of patients, and there were no grade 4 or 5 events during therapy.

Outcome

With a median follow up of 7.7 years, 57 of 106 patients (54%) have developed tumor recurrence and 28 of 106 patients (26%) have died. The 1, 3, and 5 year RFS rate is 96, 60, and 40%, with a median of 4.0 years (Figure 2A). Notably, only 4 patients developed tumor recurrence during their first year in the study. Univariable analysis showed that small bowel site and a high mitotic rate conferred lower RFS (Table 4). The type of mutation was also important. RFS was lowest (median 19 months) in patients with a *KIT* exon 9 mutation, while patients with a *KIT* exon 11 mutation had a median RFS of 42 months (Figure 2B). In contrast, patients with a *PDGFRA* mutation or a wild-type tumor fared better, although these groups were small. Owing to the relatively small number of events, we constructed several exploratory models for multivariable analysis, by including both tumor size and tumor site and then one other variable. By this methodology, *KIT* exon 9 mutation (hazard ratio (HR) 5.11, 95% CI 1.84-14.14), high mitotic rate (HR 1.96, 95% CI 1.01-3.83), and age were each associated with lower RFS (Table 4).

Of the first 89 patients enrolled in the trial, 65 (73%) patients survived for 5 or more years, exceeding the a priori criterion (at least 40 (45%) patients surviving at least 5 years) for establishing the efficacy of imatinib in this patient population. The 1, 3, and 5 year OS rate based on all 106 eligible patients is 99, 97, and 83%, and the median has not been reached (Figure 3A). Univariable analysis showed that age and mitotic rate were associated with lower OS (Table 4). Patients with a *KIT* exon 9 mutation tended to have lower OS: their median survival was 54 months versus 103 months for patients with an *KIT* exon 11 mutation (Figure 3B). A multivariable analysis of OS was not performed at this point due to the small number of deaths.

DISCUSSION

This was the first trial ever to test the benefit of adjuvant imatinib for GIST. We defined “high risk” for recurrence by tumor size, tumor rupture, and limited peritoneal disease. Tumor size is known to be associated with outcome in GIST.[12] Certainly, some of the patients in this trial with large tumors would currently be offered neoadjuvant imatinib to facilitate tumor resection. Tumor rupture was previously reported to be associated with a greater than 90% chance of recurrence in a historical series of gastrointestinal

“leiomyosarcomas,” most of which were probably GISTs.[16] Patients with limited peritoneal metastases from GIST (13% in this series) are now generally treated as having metastatic GIST and so would be excluded from current trial designs of adjuvant therapy. We found that patients with tumor rupture or limited peritoneal metastases did not actually have lower RFS in this trial, perhaps because the entire patient population was at high risk of recurrence anyway. Mitotic rate is the dominant pathologic predictor of outcome in patients with primary GIST treated with surgery alone.[12] However, because of the lack of standardization in measuring mitotic rate,[2] we chose not to include it in the eligibility criteria. Within our high risk population, we found mitotic rate measured retrospectively to be associated with RFS and OS, but with a much smaller hazard ratio than in unselected populations of GIST patients.[12] Since the design of this trial, a number of classification systems[17-19] have been adopted to assess postoperative risk of recurrence in GIST. The most widely accepted is the Miettinen classification, according to which there were 41 moderate risk patients and 57 high risk patients in the present series. As expected, patients at high risk by the Miettinen classification had worse outcome, with a median RFS of 36 months and a median OS of 103 months.

Although tumor mutation status is prognostic for survival and predicts the response to imatinib in GIST treatment, none of the current prognostic systems actually include tumor mutation status. We found that patients with a *KIT* exon 9 mutation had lower RFS than those with either a *KIT* exon 11 mutation or no detectable mutation. This is consistent with data in metastatic GIST where patients with a *KIT* exon 9 mutation had worse outcomes compared to patients with a *KIT* exon 11 mutation.[20, 21] In our primary high risk patients, the rate of *PDGFRA* mutation (13%) was much higher than that reported in metastatic GIST, as has been found by others,[22] suggesting that these tumors are less likely to recur. These patients fared relatively well in terms of RFS.

Previously, we reported the results of a large (n=713 patients), phase 3, placebo-controlled trial testing adjuvant imatinib following the resection of localized, primary GIST at least 3 cm in size.[3] We compared assignment to 1 year of adjuvant imatinib to placebo. After a median followup of 19.6 months, the 1 year RFS rate was greater on the imatinib arm (98 vs. 83%, $p<0.0002$). These results culminated in the approval of adjuvant imatinib for GIST by the Food and Drug Administration (FDA) in December 2008 and changed the standard of care in many places in the world. Although there is no comparison arm in the present study, we know from the Z9001 trial that in patients with tumors >10 cm, RFS was longer on the imatinib arm than the placebo arm (90 vs. 55% at 2 years). As in the Z9001 study, the rate of recurrence in the present trial was minimal during the year of prescribed therapy but markedly increased after 18 months (i.e., 6 months after completing the prescribed therapy) following study entry. Longer follow up in the Z9001 trial should reveal how often imatinib is actually curative. It should be noted in the present study that recurrences still occurred after 4 years, which underscores the importance of continued radiologic surveillance.

While imatinib dramatically increased RFS in ACOSOG Z9001, there was no difference in OS between the arms, possibly due to the modest length of follow up or the trial design, which permitted crossover to imatinib for patients who developed recurrence on the placebo arm. Longer follow up is needed to determine whether overall survival is improved by

taking imatinib immediately after surgery as opposed to waiting until tumor recurrence. It is noteworthy that in the current study there were just a few deaths within the first 3 years, after which the mortality rate increased considerably. The OS rate was 83% at 5 years, which greatly exceeds historical data and is consistent with the median survival in advanced GIST being 4 years at present.[11] The optimal duration of adjuvant imatinib therapy in GIST is uncertain. Given the increase in the rate of recurrence that developed in both Z9000 and Z9001 patients at approximately 18 months (6 months after the prescribed dose ended), 1 year of therapy seems inadequate, at least if the goal is to maximize RFS. Longer treatment may be indicated in patients with a *KIT* exon 9 mutation, as this group did not develop recurrence in the first year but did thereafter. It is possible that patients with a *KIT* exon 9 mutation would do better with higher dose imatinib (e.g., 800 mg/day), since this dose appears to delay progression in metastatic GIST.[11] The European Organization for Research and Treatment of Cancer (EORTC) has sponsored an open label, randomized trial (NCT00103168) comparing 0 versus 2 years of adjuvant imatinib in intermediate and high risk GIST. No data are available at this time. Joensuu and colleagues have recently published data from the Scandinavian Sarcoma Group SSGXVII trial (NCT00116935), in which patients with GIST deemed to be at high risk of recurrence were randomized to 1 or 3 years of adjuvant imatinib and followed for a median of 4.5 years.[23] RFS was greater in patients assigned to 3 years of therapy. OS was also increased but there were relatively few deaths (9% of population); meanwhile, there was no difference in disease-specific survival. Because it was likely that 3 years of therapy would prove superior to 1 year in terms of RFS, we initiated and have already accrued patients to a phase II trial (NCT00867113) of 5 years of adjuvant imatinib for treatment of moderate to high risk tumors. Thus, the long-term use of adjuvant imatinib may become analogous to chronic hormonal therapy use in breast cancer. At this point, there is general consensus that adjuvant imatinib is not indicated in patients at low risk of tumor recurrence.

In conclusion, for patients with high risk GIST, it is clear that 1 year of adjuvant imatinib prolongs RFS and OS. With 1 year of prescribed adjuvant imatinib, the 5 year survival is 83% compared to 35% in historical controls. Tumor size, small bowel site, *KIT* exon 9 mutation, high mitotic rate, and age were associated with RFS, while age and mitotic rate correlated with OS. Adjuvant imatinib was well tolerated, as we and others have documented previously.[15, 23] However, discontinuation of therapy coincides with an increased rate of tumor recurrence.

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Figure 1.
CONSORT diagram.

Figure 2. Recurrence-free survival. Figure 2A. Entire population. Figure 2B. Mutation status.

Figure 3.
 Overall survival. Figure 3A. Entire population. Figure 3B. Mutation status.

Table 1

Clinicopathologic features.

Characteristic	N = 106 patients
Sex, n (%)	
Male	60 (57)
Female	46 (43)
Age, years	
Median	58
Min, Max	19, 79
ECOG performance status, n (%)	
0	75 (71)
1	31 (29)
Time from operation to 1 st dose, days	
Median	59
Min, Max	25, 84
Tumor size, cm	
Median	13
Min, Max	3, 42
Tumor size ≥ 10 cm, n (%)	89 (85)
Tumor rupture, n (%)	18 (17)
1-4 peritoneal metastases, n (%)	14 (13)
Tumor origin, n (%)	
Stomach	53 (50)
Small intestine	45 (42)
Rectum	1 (1)
Other	7 (7)
Microscopic margins, n (%)	
Negative	94 (90)
Positive	10 (10)
Unknown	2
Mitotic rate [^] , n (%)	
<5	41 (52)
5	38 (48)
unknown	27
Mutation, n (%)	

Characteristic	N = 106 patients
<i>KIT</i> exon 11	45 (58)
<i>KIT</i> exon 9	10 (13)
<i>KIT</i> exon 13	4 (5)
<i>PDGFRA</i>	10 (13)
Wild-type	9 (12)
Unknown	28

[^]
per 50 high powered fields

Table 2

Tumor mutation status.

	Gender			Mitotic Rate			Location		
	Male	Female	<i>p</i>	<5	5	<i>p</i>	Stomach	Small Int	<i>p</i>
<i>KIT</i>									
Exon 9	7 (16.7%)	3 (8.3%)	0.3209	3 (11.5%)	6 (17.6%)	0.0086	0 (0.0%)	9 (27.3%)	0.0007
Exon 11	24 (57.1%)	21 (58.3%)		8 (30.8%)	22 (64.7%)		23 (59.0%)	18 (54.6%)	
Exon 13	1 (2.4%)	3 (8.3%)		2 (7.7%)	1 (2.9%)		2 (5.1%)	1 (3.0%)	
<i>PDGFRA</i>	7 (16.7%)	3 (8.3%)		8 (30.8%)	1 (2.9%)		9 (23.1%)	1 (3.0%)	
WT	3 (7.1%)	6 (16.7%)		5 (19.2%)	4 (11.8%)		5 (12.8%)	4 (12.1%)	
Unknown*	18	10		15	4		14	12	

* Due to unknown mitotic rate or mutation status

Table 3

Adverse events.

		Total	Grade 1	Grade 2	Grade 3
Heme	Neutropenia	13 (12%)	5 (4%)	5 (4%)	3 (2%)
GI	Abdominal pain	29 (27%)	20 (18%)	6 (5%)	3 (2%)
	Nausea	52 (49%)	39 (36%)	9 (8%)	4 (3%)
	Vomiting	22 (21%)	15 (14%)	6 (5%)	1 (1%)
	Diarrhea	54 (51%)	40 (37%)	12 (11%)	2 (1%)
	ALT or AST elevation	30 (28%)	21 (20%)	5 (4%)	4 (3%)
Skin	Dermatitis	39 (36%)	26 (24%)	9 (8%)	4 (3%)
Other	Fatigue	55 (52%)	44 (41%)	9 (8%)	2 (1%)
	Edema	60 (57%)	44 (41%)	16 (15%)	0 (0%)

ALT – alanine aminotransferase; AST – aspartate aminotransferase

Table 4

Prognostic factors.

RFS Models				
	Univariable		Multivariable[*]	
Characteristic	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	1.02 (1.00 – 1.04)	0.052	1.03 (1.01 – 1.05)	0.011
Gender				
male	1.00 (ref)	0.48	1.03 (0.57 – 1.85)	0.93
female	0.83 (0.49 – 1.40)			
Tumor size	1.02 (0.99 – 1.06)	0.14	1.04 (1.00 – 1.08)	0.031
Tumor site				
stomach	1.00 (ref)	0.006	2.93 (1.55 – 5.34)	0.0009
small bowel	2.18 (1.25 – 3.79)			
Mitotic rate [^]				
< 5	1.00 (ref)	0.008	1.96 (1.01 – 3.83)	0.047
5	2.26 (1.23 – 4.13)			
Mutation				
<i>KIT</i> exon 11	1.00 (ref)		1.00 (ref)	
<i>KIT</i> exon 9	6.03 (2.47 – 14.73)		5.11 (1.84 – 14.14)	
<i>KIT</i> exon 13	1.62 (0.48 – 5.49)	0.0002	1.84 (0.42 – 8.18)	0.013
<i>PDGFRA</i>	0.64 (0.24 – 1.70)		1.63 (0.50 – 5.35)	
Wild-type	0.43 (0.13 – 1.44)		0.49 (0.14 – 1.75)	

OS Models		
	Univariable	
Characteristic	HR (95% CI)	p-value
Age	1.04 (1.01 – 1.08)	0.005
Gender		
male	1.00 (ref)	0.8
female	0.91 (0.43 – 1.92)	
Tumor size	1.04 (0.99 – 1.08)	0.13
Tumor site		
stomach	1.00 (ref)	0.055
small bowel	2.19 (0.98 – 4.89)	
Mitotic rate [^]		

OS Models		
	Univariable	
Characteristic	HR (95% CI)	p-value
< 5	1.00 (ref)	0.011
5	3.35 (1.32 – 8.51)	
Mutation		0.25
<i>KIT</i> exon 11	1.00 (ref)	
<i>KIT</i> exon 9	2.34 (0.83 – 6.59)	
<i>KIT</i> exon 13	0.00 (0.00 – .)	
<i>PDGFRA</i>	0.53 (0.12 – 2.35)	
Wild-type	0.32 (0.04 – 2.44)	

ref – reference; HR – hazard ratio; CI – confidence interval

[^]
per 50 high powered fields,

^{*}
multivariable models include tumor size, tumor site, and the indicated variable.