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Original Articles

Prospective Observational Study of Imatinib Therapy in Japanese Patients with Advanced Gastrointestinal Stromal Tumors: Long-term Follow-up and Second Malignancy

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Objective: Limited data are available concerning long-term results of imatinib therapy in patients with advanced gastrointestinal stromal tumors. We aimed to clarify the long-term outcomes of imatinib therapy in Japanese patients with advanced gastrointestinal stromal tumors.

Methods: A prospective, observational study of imatinib therapy for unresectable and metastatic gastrointestinal stromal tumors was conducted in our institution. Imatinib was initiated at a dose of 400 mg daily and continued until disease progression. Safety, efficacy and long-term tolerability and survival were evaluated in an intent-to-treat population. The median follow-up period in this study was 68 months.

Results: Seventy patients were enrolled between December 2001 and December 2009. Treatment-related Grade 3/4 adverse events occurred in 49 patients (70.0%). Although 14 patients required adverse effect management with hospitalization, only 5 patients (7.1%) withdrew from the treatment owing to imatinib intolerance. The tumor response and clinical benefit rates were 61.4 and 85.7%, respectively. Thirty-seven patients (52.9%) maintained the treatment at 400 mg daily imatinib, whereas 33 patients (47.1%) had their dose reduced to 300 mg daily or less. The overall survival rate at 5 years was 60.9% and the median survival time was 70 months. The median progression-free survival time of all the 70 enrolled patients was 30 months. Seven patients (10.0%) suffered from second malignancies, including three patients with genitourinary carcinomas.

Conclusions: Despite the need for dose reduction, the long-term results of imatinib therapy for advanced gastrointestinal stromal tumors were good in Japanese patients. Physicians should pay attention to the occurrence of second malignancies during imatinib therapy for gastrointestinal stromal tumor patients.

Key words: gastrointestinal stromal tumor – imatinib mesylate – long-term outcomes – molecularly targeting therapy – second malignancies

INTRODUCTION

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal neoplasm of the gastrointestinal tract. More than 90% of the GISTs express KIT kinase (CD117), and the constitutive activation of this protein, which is caused by gene mutations, plays a pivotal role in the development of GISTs (1).

This understanding of the molecular basis of the GIST pathogenesis has lead to the clinical introduction of tyrosine kinase inhibitors to the treatment for advanced GISTs 10 years previously (2). Imatinib mesylate is a selective tyrosine kinase inhibitor that is active against BCR-ABL, KIT and platelet-derived growth factor receptor α (PDGFRA). This molecularly targeting drug shows a potent antitumor effect on GISTs and is now the standard of treatment for patients with unresectable and/or metastatic GISTs (3–5).

Imatinib therapy has markedly improved the prognosis of patients with advanced GISTs, for which conventional chemotherapy is ineffective. However, the molecularly targeting drug has a unique and clinically unfavorable feature. Despite the high efficacy of imatinib, it is exceptional that patients show a histological complete response (CR) to imatinib therapy alone (6), and even when they do, discontinuation of imatinib leads to a relapse of the disease inevitably (6–8). Thus, the current consensus is that imatinib therapy for advanced GISTs should be continued until the disease has progressed (3,4).

However, the data concerning long-term outcomes of imatinib therapy for advanced GIST patients are very limited. Available so far are only the results of the B2222 study (9), a large-scale Phase II trial that was conducted in the USA and Finland. Blanke et al. (10) have reported the long-term follow-up data of 147 patients enrolled in the B2222 study. In that study, 31% of the patients continued to take the drug for more than 5 years and the median survival time (MST) of all the patients was 57 months with a median follow-up time of 63 months, indicating that imatinib therapy is tolerable for a long time and the long-term survival is good with antitumor effect in the short term. These findings strongly support the consensus that imatinib therapy should be the first choice of treatment for unresectable and metastatic GISTs. However, as selected patients are generally enrolled in clinical trials to obtain unequivocal and conclusive results (11), it still remains unclarified whether the excellent results shown in the B2222 study can be expected in the general patient population with advanced GISTs. Furthermore, a Phase II trial of Japanese patients with advanced GISTs (12) has shown that Grade 3 adverse effects occurred in 54% of the patients who underwent imatinib therapy, although those were generally manageable. The incidence of serious adverse events (SAE) is significantly higher in the trial of Japanese patients than those in trials of imatinib therapy conducted in western countries (9,13). The high incidence of adverse effects associated with imatinib may lower the efficacy of imatinib therapy and may affect the survival of patients unfavorably in the long-term for Japanese or East Asian patients.

To determine the efficacy and safety of imatinib therapy for Japanese patients with advanced GISTs, we started a prospective study in 2001. In this study, we prospectively accumulated the data on safety, efficacy and survival of patients who underwent imatinib therapy for unresectable and/or metastatic GISTs in our hospital. Here, we present the long-term outcomes of imatinib therapy in Japanese GIST patients in this prospective study and also examine the occurrence of second malignancies during imatinib therapy.

PATIENTS AND METHODS

Study Design and Patients

This study was designed as a prospective observational study in a single institution, with the aim of evaluating the clinical efficacy and safety of imatinib therapy for Japanese patients with advanced GISTs. Japanese patients with unresectable and/or metastatic GISTs were recruited from December 2001. The inclusion criteria were as follows: (i) histologically proven GIST; (ii) having at least one measurable lesion detected by computed tomography (CT) or magnetic resonance imaging (MRI); (iii) an Eastern Cooperative Oncology Group performance status of 0–2; and (iv) adequate organ function. No age limit was set and target accrual was 60 patients.

The study was approved by the institutional review board of Niigata University Graduate School of Medical and Dental Sciences, and written informed consent was obtained from all the patients.

Pathological Diagnosis

On enrollment, the diagnosis of GIST in each patient was based on the histological diagnosis by the pathologists at a local hospital where the patient underwent surgery for primary tumors. We predetermined that patients with KIT-negative GIST were also eligible to participate in this study when their tumor was positive for CD34 and the morphological features of the tumor were compatible with GIST. Three patients with KIT-negative tumors were enrolled in this study. The tumors of these three patients were reviewed by an experienced pathologist (S.H.) after the initiation of the treatment, and the final diagnoses of these patients were GIST with *PDGFRA* mutation, leiomyosarcoma and unclassified sarcoma. In this study, the two patients with non-GIST sarcoma were also analyzed as the intent-to-treat population.

Treatment and Dose Modification

Imatinib therapy was started at a dose of 400 mg once a day, regardless of age, sex or stature. The treatment was continued until progression of disease (PD), unacceptable toxicity

or patients' refusal. We assessed patients at weeks 2, 4, 8 and 12, and then at 2- to 3-month intervals by physical examination, complete blood count with differential count and routine biochemical examinations. Adverse effects were graded on the basis of the National Cancer Institute common terminology criteria for adverse events, version 2.0. The dose was modified for non-hematological Grade 3 or 4 events, repeating hematological Grade 3, or when patients claimed that the dose was intolerable. Hypophosphatemia was not considered to be an adverse event requiring dose modification in this study. We defined 300 mg daily as the minimal treatment dose and made effort to maintain the administration of imatinib at 300 mg daily or higher.

Patients showing PD underwent molecularly targeting therapy with other tyrosine kinase inhibitors, salvage surgery, interventional radiology and/or best supportive care. The selection of the second-line treatment was left to the attending physician. The dose escalation of imatinib to 600–800 mg/day was not adopted in this study.

Follow-up and Evaluation

All the patients were followed at our hospital. Adverse events were examined at each visit of the patient until PD and their relationship with the treatment was evaluated. The maintenance dose was defined in this study as the daily dose of imatinib that was used for the longest period until PD.

CT with intravenous contrast or MRI of the abdomen and pelvis was carried out 1, 3 and 6 months after the initiation of treatment, and every 6 months thereafter or whenever medically indicated. Antitumor responses were assessed on the basis of the Response Evaluation Criteria in Solid Tumors (RECIST) criteria (14). CR and partial response (PR) were confirmed by repeated imaging at week 4 or later. Stable disease (SD) was defined as neither CR, PR nor PD, and the diseases showed no significant change for at least 12 weeks.

Data and Statistical Analysis

Data on safety, efficacy and survival of the patients were prospectively described in medical charts and case report forms and regularly recorded in patient files. The date of cut-off for this study was 7 February 2012. The median follow-up period of living patients was 68 months (maximum, 122 months).

The overall and progression-free survival (PFS) times were estimated by the Kaplan–Meier method. The overall survival time was defined as the time from the initiation of the first dose of imatinib to death from any cause. Patients who did not die were censored on the last date they were known to be alive. The PFS time was defined as the time from the initiation of the first dose of imatinib to PD or death from any cause. In this study, PD included focal progression, i.e. nodular regrowth that emerged in degenerated lesions, with a significant increase in contrast enhancement. All analyses were performed using Statistical Analysis Software (version 8.0; SAS Institute, Cary, NC, USA).

RESULTS

Patients

Between December 2001 and December 2009, 70 patients with unresectable and/or metastatic GISTs were enrolled in this study. The demographics of the 70 patients are listed in Table 1.

Safety

Adverse effects related to imatinib therapy were found in 69 of the 70 patients enrolled. The most frequent adverse effect was edema (88.6%), followed by anemia (81.4%), hypophosphatemia (72.9%), leukopenia (68.6%), neutropenia (62.9%), nausea (62.9%) and eosinophilia (60%). Grade 3 or higher-grade adverse effects related to the treatment occurred in 49 patients (70.0%), with hypophosphatemia (25.7%) being the most frequent, followed by anemia (12.9%) leukopenia (11.4%), rash (10.0%) and neutropenia (8.6%). Excluding hypophosphatemia, the incidence of Grade 3/4 adverse effects were 61.4%. Although most of the adverse effects were manageable in outpatient clinics, 14 patients (20.0%) required hospitalization for the management of the SAE: Grade 3 nausea (2), gastrointestinal bleeding (2), tumor bleeding (2), congestive heart failure (2), interstitial pneumonitis (2), edema (1), anemia (1), febrile neutropenia (1) and bacteremia (1). There was no treatment-related death in this cohort. In Table 2, we summarize the treatment-related adverse effects that occurred in more than 10% of the patients.

Antitumor Efficacy

Of the 70 enrolled patients, 7 showed CR (10.0%), 36 PR (51.4%), 17 SD (24.3%) and 6 PD (8.6%). In four patients, their responses were not evaluated because the patients underwent resection of the target lesions before the determination of their antitumor response: one patient underwent surgery on day 25 because of an imatinib-induced bleeding from a large peritoneal deposit. In the remaining three patients who had resectable liver oligometastasis, the required protocol treatment was discontinued and surgery was selected because of febrile neutropenia, financial problems and poor response at the first evaluation. The response rate in this study was 61.4% and the clinical benefit rate (CR + PR + SD) was 85.7%.

Survival

The overall survival rates were 91.4% at 1 year, 74.1% at 3 years and 60.9% at 5 years, and the MST was 70 months in all the 70 enrolled patients (Fig. 1). With a median follow-up

Table 1. Characteristics of all 70 patients enrolled

	No. of patients
Age (years)	
Median	64
Range	39–85
<70	40
≥70, <80	23
≥80	7
Gender	
Male	38
Female	32
ECOG PS	
0	38
1	23
2	9
Body weight (mean ± SD, kg)	
Male	59.2 ± 9.9
Female	47.7 ± 6.0
Site of primary disease	
Stomach	33
Duodenum	7
Jejunum/ileum	25
Colon/rectum	5
Surgery for GIST (time)	
0	12
1	38
2	11
≥3	9
Disease	
Unresectable	3
Metastatic	67
Site of tumor metastasis[a]	
Liver	49
Peritoneum	30
Bone	3
Others[b]	10
KIT expression	
Positive	67
Negative	3
Kinase mutation	
KIT exon 11	20
KIT exon 9	5
PDGFRA exon 18	1
Wild-type	2
Unknown	42

ECOG PS, Eastern Cooperative Oncology Group performance status; SD, standard deviation; GIST, gastrointestinal stromal tumor; PDGFRA, platelet-derived growth factor receptor α-gene.
[a]Twenty-three patients had tumors at more than one site.
[b]Including adrenal, lymph node, lung, pleura, retroperitoneum and thyroid.

Table 2. Adverse effects related to imatinib therapy

	Any grade, *n* (%)	Grade 3 or 4, *n* (%)
Any adverse effects		
Possibly related to the treatment	69 (98.6)	49 (70.0)
Hematologic		
Anemia	57 (81.4)	9 (12.9)
Leukopenia	48 (68.6)	8 (11.4)
Neutropenia	44 (62.9)	6 (8.6)
Thrombocytopenia	40 (57.1)	1 (1.4)
Non-hematologic gastrointestinal		
Nausea	34 (48.6)	2 (2.9)
Diarrhea	22 (31.4)	0 (0.0)
Anorexia	18 (25.7)	0 (0.0)
Vomiting	13 (18.6)	0 (0.0)
Stomatitis	9 (12.9)	1 (1.4)
Dysgeusia	7 (10.0)	0 (0.0)
Liver		
Hypoalbuminemia	35 (50.0)	0 (0.0)
AST	30 (42.9)	0 (0.0)
ALT	17 (24.3)	0 (0.0)
ALP	12 (17.1)	0 (0.0)
γ-GPT	10 (14.3)	0 (0.0)
Dermatology		
Rash	25 (35.7)	8 (11.4)
Alopecia	11 (15.7)	0 (0.0)
Investigations		
Hypophosphatemia	51 (72.9)	18 (25.7)
Hypocalcemia	46 (65.7)	1 (1.4)
Hypokalemia	32 (45.7)	0 (0.0)
Hyponatoremia	18 (25.7)	1 (1.4)
Hyperkalemia	8 (11.4)	1 (1.4)
Eosinophil increased	42 (60.0)	0 (0.0)
Amylase level increased	23 (32.9)	0 (0.0)
Others		
Edema	62 (88.6)	2 (2.9)
Muscle cramp	24 (34.3)	1 (1.4)
Creatinine	20 (28.6)	0 (0.0)
Conjunctival hemorrhage	14 (20.0)	0 (0.0)
Pleural effusion, non-malignant	10 (14.3)	1 (1.4)

Adverse effects that occurred in more than 10% of the patients are listed.
AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; γ-GPT, γ-glutamyltranspeptidase.

time of 68 months, 30 patients were surviving for 60 months or longer.

The PFS rates of all the 70 patients were 70.3% at 1 year, 46.0% at 3 years and 32.9% at 5 years. The median PFS was

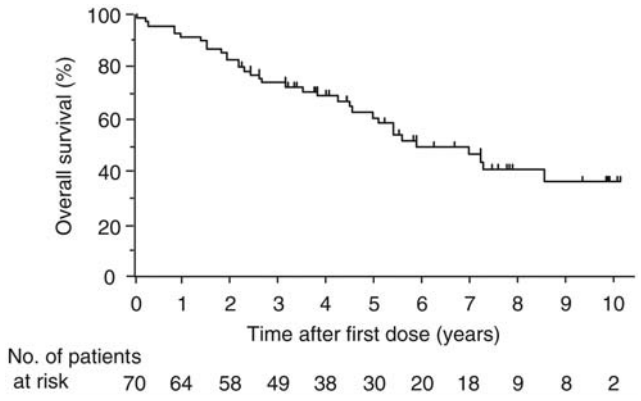

Figure 1. The Kaplan–Meier estimates of overall survival of all 70 patients enrolled. The 1-, 3- and 5-year overall survival rates were 91.4, 74.1 and 60.9, respectively. The overall median survival time was 70 months.

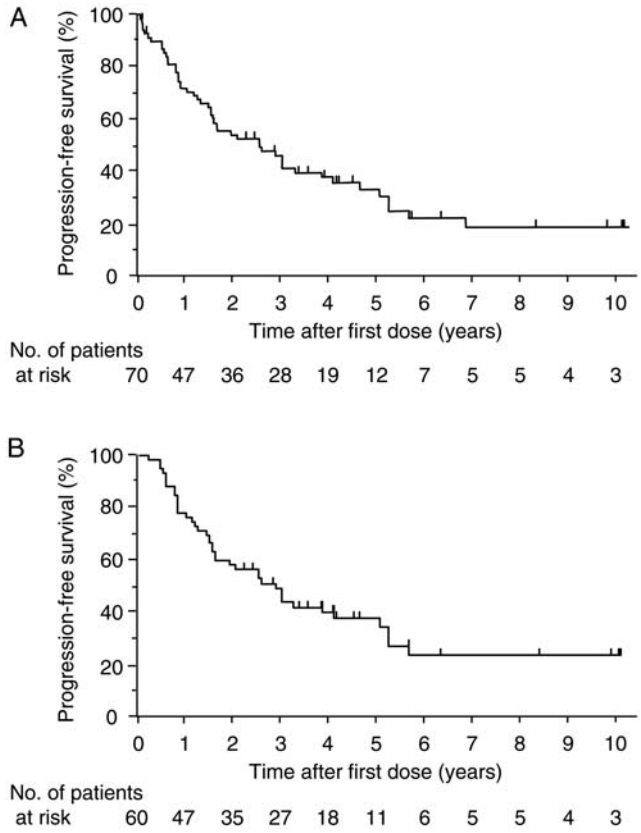

Figure 2. The Kaplan–Meier estimates of progression-free survival (PFS) of all 70 patients enrolled (A) and 60 patients who showed complete response, partial response and stable disease (B). The median PFS was 30 and 34 months, respectively.

30 months (Fig. 2A). To determine how long imatinib therapy can control advanced GISTs, we also analyzed the PFS of 60 patients who showed CR, PR or SD. The PFS rates of the 60 patients were 76.7% at 1 year, 49.5% at 3 years and 37.9% at 5 years. The median PFS was 34 months (Fig. 2B).

Treatment After Progression

As of the data cut-off date, 46 patients showed PD, which included secondary resistance to imatinib. Second-line treatments for these PD patients were surgical resection of the resistant tumors in 13, transcatheter arterial chemoembolization in 10, sunitinib therapy in 7 and palliative imatinib therapy in 16.

Tolerability in the Long Term

The maintenance doses of imatinib were 400 mg/day in 37 patients (52.9%), 300 mg/day in 28 patients (40.0%) and $<$300 mg/day in 5 patients (7.1%). In the 60 patients who showed clinical benefits, the median treatment duration was 45 months (maximum, 122 months).

On the date of data cut-off, 20 patients (28.6%) were on imatinib therapy, whereas the remaining 50 patients (71.4%) discontinued the therapy. Fourteen patients were continuing imatinib therapy at the age of 80 years or older.

The causes of the discontinuation included PD in 38 patients and death caused by an other disease in 1. The remaining 11 patients (15.7%) withdrew from the treatment before PD or death: 5 patients showed imatinib intolerance (7.1%), 3 patients with CR (4.3%) and 3 patients had financial problems regarding long-term treatment (4.3%). The treatment durations and the age at discontinuation of the five imatinib-intolerant patients were 3, 33, 36, 45 and 50 months, and 75, 77, 69, 81 and 78 years, respectively (Table 3).

Second Malignancy

In the study period, seven patients (10.0%) suffered from second malignancies: urinary bladder carcinoma (two), renal cell carcinoma (one), plasmacytoma of the bone (one), squamous cell carcinoma (SCC) of the lungs (one), SCC of the esophagus (one) and gastric adenocarcinoma (one). Although the patient with esophageal SCC died of the second malignancy, the other patients were able to continue imatinib therapy following the treatment of their second malignancies. We show the features of the seven patients with second malignancies in Table 4.

DISCUSSION

We here presented the results of a 10-year observational study of 70 GIST patients who underwent imatinib therapy in our hospital. The median follow-up period was 68 months in this study. This relatively long follow-up period of the patients allowed us to address several unsolved and clinically important questions, including long-term tolerability, long-term survival and second malignancies.

BFR14 (8), a randomized controlled trial conducted by a French sarcoma group, has shown that the discontinuation of imatinib therapy causes a rapid exacerbation of tumors even

Table 3. Long-term tolerability of imatinib therapy in 70 GIST patients

	No. of patients (%)
Maintenance dose[a]	
400 mg daily	37 (52.9)
300 mg daily	28 (40.0)
<300 mg daily[b]	5 (7.1)
Status of the treatment	
Ongoing	20 (28.6)
Discontinued	50 (71.4)
PD/death	39 (55.7)
Intolerance	5 (7.1)
CR	3 (4.3)
Financial	3 (4.3)

PD, progressive disease; CR, complete response.
[a]Daily dose of imatinib that was used for the longest period until PD.
[b]Two hundred milligrams daily in three patients and 300 mg/day with regular off-drug in two patients.

Table 4. Patients with second malignancies

Patient	Age[a]	Sex	Second malignancy	Interval[b] (months)	Treatment	Status
1	67	M	Urinary bladder carcinoma	37	TUR	Surviving on SU
2	63	M	Renal cell carcinoma	32	Surgery	Surviving on IM
3	82	M	Plasmacytoma	53	Surgery	DOG
4	77	M	Lung SCC	21	RT	DOG
5	78	F	Esophageal SCC	17	EMS	DOS
6	59	M	Gastric adenocarcinoma	61	ESD	Surviving on IM
7	84	M	Urinary bladder carcinoma	19	TUR	Surviving on IM

TUR, transurethral resection; SU, sunitinib; IM, imatinib; DOG, died of gastrointestinal stromal tumor; SCC, squamous cell carcinoma; RT, radiotherapy; EMS, esophageal metallic stenting; DOS, died of second malignancy; ESD, endoscopic submucosal dissection.
[a]Ages at diagnosis of secondary malignancies.
[b]The interval between the initiation of imatinib therapy and the time of diagnosis of second malignancy.

after a 3-year treatment. Additionally, the French group has very recently reported that the trial with discontinuation after a 5-year treatment reproduced very similar findings to those of the 3-year treatment trial (15). On the basis of this clinical evidence, GIST clinical guidelines in many countries (3–5) recommend that imatinib therapy for advanced GISTs should be continued until the disease has apparently progressed. However, it remains a great concern among practitioners whether imatinib can be administered for a long time, i.e. up to 5 years, because patients become older as the treatment goes well and a significantly large number of patients experienced adverse effects during the treatment. This concern was addressed in the present study, which showed favorable results about long-term tolerability.

Only five patients (7.1%) discontinued the treatment owing to imatinib intolerance, with a median treatment duration of 45 months in the 60 patients who showed clinical benefits in this study. This finding indicates a fairly good tolerability to anticancer treatment in the long term, when compared with conventional chemotherapy. Furthermore, 14 patients aged over 80 years stably maintained their treatment. Imatinib is a molecularly targeting drug that competitively inhibits the phosphorylation of KIT, BCR-ABL and PDGFRA. The nature of high selectivity may account for enabling the long-term use in GIST patients.

The second clinically important finding of the present study is that the long-term survival of Japanese patients with advanced GISTs was as good as those of patients in western countries. Although there have been many studies concerning imatinib therapy for advanced GISTs so far, information on long-term survival of patients is very limited, as imatinib has yet only a 10-year history of practice for GISTs.

Demetri et al. (16) have pointed out the importance of maintaining the plasma imatinib level in GIST treatment. They divided their 107 patients into four groups according to the plasma level of imatinib and analyzed the time to progression (TTP) of each group. In their study, the lowest quartile of the patients showed a significantly shorter TTP than the other three quartiles (11.3 vs. 30.6–33.1 months). In addition, the Phase II clinical trials of imatinib therapy in Korea (17) and Japan (12) revealed that Grade 3 hematological adverse effects more frequently occurred in Asian patients than in patients in western countries. The high susceptibility to imatinib-induced hematological toxicities particularly observed in Asian patients often requires dose reduction and has been a great concern among clinicians because it may lower the treatment intensity and consequently shorten patients' survival in the long term.

The findings of the present study have addressed such a concern of imatinib therapy for East Asian patients. Although nearly one-half of the patients in this study required a reduction in their maintenance dose of imatinib, the MST was as long as 70 months. It was unexpectedly longer than the MST of 57 months in the B2222 study (10), a large-scale, early Phase II trial of imatinib therapy for advanced GISTs.

The following explanations may account for the longer survival time of the patients in the present study. First, we could utilize critical information about the management of GIST patients undergoing imatinib therapy from preceding studies: imatinib should be continued as long as possible (8,15) and surgical intervention may benefit patients with limited progression (7,18,19). Secondly, sunitinib, a second-line tyrosine kinase inhibitor for imatinib-resistant GIST, was available for many of the patients of this study because

the drug was already approved. Thirdly, the mean body weights of the patients in the present study were 59.2 kg in men and 47.7 kg in women. The small stature of Japanese patients may relatively increase the imatinib plasma level and be favorable in terms of the antitumor effect. Although we do not recommend imatinib therapy at a lower dose for Japanese patients, this study may support the understanding that it is reasonable to determine imatinib dose on the basis of the assessment of side effects in each patient.

Second malignancies are potential side effects of anticancer agents used in the long term. No study has addressed this clinically important issue in imatinib therapy for GIST patients so far.

In this study, we encountered seven patients who suffered from second malignancies during imatinib therapy. The incidence of 10% in our study, with a median follow-up period of 68 months, appears to be somehow higher than that in the general population, because the prevalence of malignancy in Japanese aged 65–69 years in 2005 was estimated as 1196 per 100 000 annually (20). Additionally, we should pay particular attention to the types of the second malignancies found in our study. Of the seven second malignancies found in this study, three were carcinomas of the urinary system, two urinary bladder carcinomas and one renal cell carcinoma. *In vivo* experiments revealed that rats exposed to imatinib for 2 years showed a significantly increased risk of carcinogenesis in the genitourinary system (21). Further study is required to determine whether imatinib may increase second cancer risk in GIST patients.

Second cancer risk in GIST patients should also be considered from the viewpoint of the genetic background. Evidence that GIST patients are likely to develop other malignancies has been recently accumulating (22–24). Agaimy et al. (22) collected 4813 GIST cases with informative data by reviewing the literature. In their study, the overall frequency of second malignancy was estimated to be 13%. In addition, Pandurengan et al. (23) have reported, on the basis of the cancer registry of their institution, that 153 (20%) of 783 GIST patients synchronously or metachronously developed additional primary malignancies. Interestingly, in their study, genitourinary carcinomas accounted for 33% of their cases and were the most frequent malignancies, which are in agreement with our study. Unfortunately, it still remains to be clarified whether the high association with other malignancies found in these studies is statistically significant. Regular check-up by urinalysis may serve as an affordable screening method for the early detection of the genitourinary carcinoma. However, what is most clinically important is to be aware of the high prevalence of second cancers in GIST patients in order to avoid misdiagnosis of symptoms caused by second malignancies, as long-term survivors are now common in patients who are undergoing imatinib therapy.

In conclusion, our prospective observational study provided useful information on clinically important issues regarding imatinib therapy for patients with advanced GISTs. This study is the first one from Asia with a long-term observation of GIST patients who underwent imatinib therapy and addressed the issue on second malignancy in this population. Imatinib therapy was well tolerated in the long term, and the overall survival was as good as that in the western trial, although nearly one-half of the patients required dose reduction. In this study, 10% of the patients suffered from second malignancies during imatinib therapy. A nationwide study will be required to clarify whether GIST patients indeed have cancer predisposition and whether there is a causal relationship between imatinib therapy and second malignancy in GIST patients.

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Conflict of interest statement

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References

1. Hirota S, Isozaki K, Moriyama Y, et al. Gain-of-function mutations of c-kit in human. *Science* 1998;279:577–80.
2. Joensuu H, Roberts PJ, Sarlomo-Rikala M, et al. Effect of the tyrosine kinase inhibitor STI571 in a patient with a metastatic gastrointestinal stromal tumor. *N Engl J Med* 2001;344:1052–6.
3. Demetri GD, von Mehren M, Antonescu CR, et al. NCCN Task Force report: update on the management of patients with gastrointestinal stromal tumors. *J Natl Compr Canc Netw* 2010;8(Suppl 2):S1–41.
4. Casali PG, Blay JY. Gastrointestinal stromal tumours: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010;21(Suppl 2):v98–102.
5. Kubota T. Gastrointestinal stromal tumor (GIST) and imatinib. *Int J Clin Oncol* 2006;11:184–9.
6. Rutkowski P, Nowecki Z, Nyckowski P, et al. Surgical treatment of patients with initially inoperable and/or metastatic gastrointestinal stromal tumors (GIST) during therapy with imatinib mesylate. *J Surg Oncol* 2006;93:304–11.
7. Gronchi A, Fiore M, Miselli F, et al. Surgery of residual disease following molecular-targeted therapy with imatinib mesylate in advanced/metastatic GIST. *Ann Surg* 2007;245:341–6.
8. Le Cesne A, Ray-Coquard I, Bui BN, et al. Discontinuation of imatinib in patients with advanced gastrointestinal stromal tumours after 3 years

of treatment: an open-label multicentre randomized phase 3 trial. *Lancet Oncol* 2010;11:942–9.
9. Demetri GD, von Mehren M, Blanke CD, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N Engl J Med* 2002;347:472–80.
10. Blanke CD, Demetri GD, von Mehren M, et al. Long-term results from a randomized phase II trial of standard- versus higher-dose imatinib mesylate for patients with unresectable or metastatic gastrointestinal stromal tumors expressing KIT. *J Clin Oncol* 2008;26:620–5.
11. Brass EP. The gap between clinical trials and clinical practice: the use of pragmatic clinical trials to inform regulatory decision making. *Clin Pharmacol Ther* 2010;87:351–5.
12. Nishida T, Shirao K, Sawaki A, et al. Efficacy and safety profile of imatinib mesylate (ST1571) in Japanese patients with advanced gastrointestinal stromal tumors: a phase II study (STI571B1202). *Int J Clin Oncol* 2008;13:244–51.
13. van Oosteron AT, Judson I, Verweij J, et al. Safety and efficacy of imatinib (STI571) in metastatic gastrointestinal stromal tumors: a phase I study. *Lancet* 2001;358:1421–3.
14. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors, European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;92:205–16.
15. Ray-Coquard IL, Bui BN, Adenis A, et al. Risk of relapse with imatinib (IM) discontinuation at 5 years in advanced GIST patients: results of the prospective BFR14 randomized phase III study comparing interruption versus continuation of IM at 5 years of treatment: a French Sarcoma Group Study. *J Clin Oncol* 2010;28(Suppl):abstr10032.
16. 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;27:3141–7.
17. Ryu MH, Kang WK, Bang YJ, et al. A prospective, multicenter, phase 2 study of imatinib mesylate in Korean patients with metastatic or unresectable gastrointestinal stromal tumor. *Oncology* 2009;76:326–32.
18. Raut CP, Posner M, Desai J, et al. Surgical management of advanced gastrointestinal stromal tumors after treatment with targeted systemic therapy using kinase inhibitors. *J Clin Oncol* 2006;24:2325–31.
19. DeMatteo RP, Maki RG, Singer S. Results of tyrosine kinase inhibitor therapy followed by surgical resection for metastatic gastrointestinal stromal tumor. *Ann Surg* 2007;245:347–52.
20. Matsuda T, Marugame T, Kamo K, Katanoda K, Ajiki W, Sobue T. Japan Cancer Surveillance Research. Cancer incidence and incidence rates in Japan in 2005: based on data from 12 population-based cancer registries in the Monitoring of Cancer Incidence in Japan (MCIJ) project. *Jpn J Clin Oncol* 2012;41:139–47.
21. Novartis. Glivec (imatinib mesylate tablets): JPN prescribing information [online]. http://product.novartis.co.jp/gli/pi/pi_glitab.pdf.
22. Agaimy A, Wünsch PH, Sobin LH, Lasota J, Miettinen M. Occurrence of other malignancies in patients with gastrointestinal stromal tumors. *Semin Diagn Pathol* 2006;23:120–9.
23. Pandurengan RK, Dumont AG, Araujo DM, et al. Survival of patients with multiple primary malignancies: a study of 783 patients with gastrointestinal stromal tumor. *Ann Oncol* 2010;21:2107–11.
24. Sevinc A, Seker M, Bilici A, et al. Co-existence of gastrointestinal stromal tumors with other primary neoplasms. *Hepatogastroenterology* 2011;58:824–30.