Sunitinib for Taiwanese patients with gastrointestinal stromal tumor after imatinib treatment failure or intolerance

Yen-Yang Chen, Chun-Nan Yeh, Chi-Tung Cheng, Tsung-Wen Chen, Kun-Ming Rau, Yi-Yin Jan, Miin-Fu Chen

AIM: To report preliminary results of the efficacy and safety of sunitinib in the management of Taiwanese gastrointestinal stromal tumors (GIST) patients facing imatinib mesylate (IM) intolerance or failure.

METHODS: Between 2001 and May 2010, 199 Taiwanese patients with metastatic GIST were treated at Chang Gung Memorial Hospital. Among them, 23 (11.6%) patients receiving sunitinib were investigated.

RESULTS: Sixteen male and 7 female patients with a median age of 59 years (range: 24-83 years) received sunitinib. Twenty-two GIST patients changed to sunitinib because of IM failure and 1 because of intolerance. The median duration of sunitinib administration was 6.0 mo (range: 2-29 mo). The clinical benefit was 65.2% (2 complete response (CR), 4 partial response (PR), and 9 stationary disease (SD); 15/23). In 12 patients harboring mutations of the kit gene at exon 11, the clinical benefit rate (CR, PR, and SD) was 75.0% and 6 patients with tumors containing kit exon 9 mutations had a clinical benefit of 50.0% (not significant, \( P = 0.344 \)). The progression free survival (PFS) and overall survival (OS) did not differ between patients whose GISTs had wild type, KIT exon 9, or KIT exon 11 mutations. Hand-foot syndrome was the most common cause of grade III adverse effect (26.1%), followed by anemia (17.4%), and neutropenia (13.0%). During the median 7.5-mo follow-up after sunitinib use, the median PFS and OS of these 23 GIST patients after sunitinib treatment were 8.4 and 14.1 mo, respectively.

CONCLUSION: Sunitinib appears to be an effective treatment for Taiwanese with IM-resistant/intolerant GISTs and induced a sustained clinical benefit in more than 50% of Taiwanese advanced GIST patients.

Abstract

AIM: To report preliminary results of the efficacy and safety of sunitinib in the management of Taiwanese gastrointestinal stromal tumors (GIST) patients facing imatinib mesylate (IM) intolerance or failure.

METHODS: Between 2001 and May 2010, 199 Taiwanese patients with metastatic GIST were treated at Chang Gung Memorial Hospital. Among them, 23 (11.6%) patients receiving sunitinib were investigated.

RESULTS: Sixteen male and 7 female patients with a median age of 59 years (range: 24-83 years) received sunitinib. Twenty-two GIST patients changed to sunitinib because of IM failure and 1 because of intolerance. The median duration of sunitinib administration was 6.0 mo (range: 2-29 mo). The clinical benefit was 65.2% (2 complete response (CR), 4 partial response (PR), and 9 stationary disease (SD); 15/23). In 12 patients harboring mutations of the kit gene at exon 11, the clinical benefit rate (CR, PR, and SD) was 75.0% and 6 patients with tumors containing kit exon 9 mutations had a clinical benefit of 50.0% (not significant, \( P = 0.344 \)). The progression free survival (PFS) and overall survival (OS) did not differ between patients whose GISTs had wild type, KIT exon 9, or KIT exon 11 mutations. Hand-foot syndrome was the most common cause of grade III adverse effect (26.1%), followed by anemia (17.4%), and neutropenia (13.0%). During the median 7.5-mo follow-up after sunitinib use, the median PFS and OS of these 23 GIST patients after sunitinib treatment were 8.4 and 14.1 mo, respectively.

CONCLUSION: Sunitinib appears to be an effective treatment for Taiwanese with IM-resistant/intolerant GISTs and induced a sustained clinical benefit in more than 50% of Taiwanese advanced GIST patients.

Key words: Sunitinib; Gastrointestinal stromal tumors; Imatinib; Failure or intolerance

Peer reviewer: I-Rue Lai, Assistant professor, Department of Anatomy and Cell Biology, Medical College, National Taiwan University, 7, Chun-San S. Rd, Taipei 106, Taiwan, China

Chen YY, Yeh CN, Cheng CT, Chen TW, Rau KM, Jan YY, Chen MF. Sunitinib for Taiwanese patients with gastrointestinal stromal tumor after imatinib treatment failure or intolerance. World J Gastroenterol 2011; 17(16): 2113-2119
Available from: URL: http://www.wjgnet.com/1007-9327/full/v17/i16/2113.htm DOI: http://dx.doi.org/10.3748/wjg.v17.i16.2113

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) primarily arise from mesenchymal tissue in the gastrointestinal (GI) tract
and abdomen. Although GISTs are rare, representing only an estimated 0.1% to 3% of all GI tract tumors[3]. GISTs account for the most common mesenchymal malignancy of the GI tract with unknown incidence.[2]. GISTs appear to be related to the interstitial cells of Cajal[8] and express the cell surface transmembrane receptor KIT, which has tyrosine kinase activity. Gain-of-function mutations of KIT are frequent in GISTs and result in constitutive activation of KIT signaling and lead to uncontrolled cell proliferation and resistance to apoptosis[15]. The KIT tyrosine kinase inhibitor imatinib mesylate (IM) has shown a promising clinical result for an advanced GIST patient[6,7], and several trials have shown a promising effect of this target therapy[6,7]. Our previous study showed that IM significantly affected survival in GIST patients[6,8].

Surgical resection remains the mainstay treatment for GIST, but recurrence is common. The 5-year survival rates for GIST after complete resection range from 40% to 65%[6,9,11,13]. Unresectable or metastatic GIST is a fatal disease that resists conventional chemotherapy. IM selectively inhibits certain protein tyrosine kinases: intracellular ABL kinase, chimeric BCR-ABL fusion oncoprotein of chronic myeloid leukemia, the transmembrane receptor KIT, and platelet-derived growth factor receptors (PDGFRs)[14-17]. IM induced a sustained objective response in more than 50% of patients with advanced GISTs in the West and in Taiwan[9,10]. However, progression of GIST eventually develops and emerges as a challenge.

Sunitinib is an oral multi-targeted tyrosine kinase inhibitor with activity against KIT and PDGFRs, as well as vascular endothelial growth factor receptors (VEGFRs), glial cell line-derived neurotrophic factor receptor (rear ranged during transfection; RET), colony-stimulating factor 1 receptor (CSF-1R), and FMS-like tyrosine kinase-3 receptor (FLT3)[18-23]. Sunitinib received multi-national approval for the treatment of GIST after failure of IM because of resistance or intolerance based on the results of an international, randomized, double-blind, placebo-controlled phase III trial[24]. The clinical safety and efficacy of both IM and sunitinib in GIST have primarily been established in Western patients living in the USA or Europe and have not been thoroughly studied in Asian patients. Fifty-six centers in 11 countries participated in the phase III trial of sunitinib in GIST, but only 15 of the 312 patients were of Asian descent (10 in the sunitinib and placebo groups, respectively)[25]. Therefore, we report our preliminary results to clarify the efficacy and safety of sunitinib in management of Taiwanese GIST patients facing IM intolerance or failure.

**Materials and Methods**

Between 2001 and May 2010, 199 patients who had histologically confirmed, recurrent, unresectable, or metastatic GIST that expressed CD117 or CD34 and were treated at the Department of Medical Oncology, and Surgery, Chang Gung Memorial Hospital were retrospectively reviewed. Failure of prior IM therapy, as demonstrated by disease progression [based on Response Evaluation Criteria in Solid Tumors (RECIST)][26] or discontinuation of IM due to toxicity was the inclusion criteria in this study. Additional eligibility criteria included an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and adequate cardiac, hepatic, renal, coagulation, and hematologic function. Key exclusion criteria included lack of recovery from the acute toxic effects of previous anticancer therapy or imatinib treatment, discontinuation of imatinib therapy within 2 wk or of any other approved or investigational drug for GIST within 4 wk before starting sunitinib treatment, clinically significant cardiovascular events or disease in the previous 12 mo, diabetes mellitus with clinical evidence of peripheral vascular disease or diabetic ulcers, or a diagnosis of any second malignancy within the previous 5 years. Patients could have previously received chemotherapeutic regimens (the last chemotherapy treatment must have been at least 4 wk before study entry) and undergone radiotherapy, or surgery, or both. The study was approved by the local institutional review board of Chang Gung Memorial Hospital, and written informed consent for drug administration and the analysis of tumor-associated genetic alteration was obtained independently from each patient.

**Study Design and Follow-up Study**

A retrospective study was conducted to evaluate the effect of sunitinib in inducing objective response in Taiwanese GIST patients. Patients were administered 50 mg (4 wk on and 2 wk off; for clinical trial) or 37.5 mg continuously of sunitinib in 12.5 mg capsules taken orally daily with food. Patients had regular physical examinations and evaluations of performance status, body weight, complete blood count, and serum chemistry. The administration of each dose and any adverse events were recorded for each patient. Standard computed tomography (CT) was performed on each patient every 3 mo for the first 3 years and every 6 mo for the following 2 years to assess patient response. Measurement of efficacy was based on objective tumor assessments made using RECIST with a minor modification to allow use of standard radiographic protocols for spiral CT. Time to response (TTR) was defined as the interval for better drug response during sunitinib treatment. Time to progression (TTP) was defined as the interval for worse drug response during sunitinib treatment. Progression free survival (PFS) was defined as no progression after sunitinib use. Overall survival (OS) was defined as survival after administration of sunitinib and death was the endpoint of the study. Response rate, PFS, OS, TTR, duration of response, and TTP were recorded. Safety and tolerability were assessed by analysis of adverse events, physical examinations, vital signs, ECOG performance status, and laboratory abnormality assessments (for example, complete blood count with differential count, serum electrolyte measurements, and electrocardiogram). Cardiac function was assessed at screening, at day 28 of
all treatment cycles, and treatment end with 12-lead electrocardiogram and multigated acquisition scans. Toxic effects were recorded in accordance with the National Cancer Institute Common Toxicity Criteria\textsuperscript{27}.

**Analysis of KIT and PDGFRα mutations**

Sections were prepared from formalin-fixed, paraffin-embedded pretreatment specimens trimmed to enrich tumor cells. Polymerase chain reaction amplification of genomic DNA for KIT and PDGFRα was performed and amplification was analyzed for mutations as previously described\textsuperscript{28}.

**Statistical analysis**

All data are presented as percentages of patients or means with standard deviation. Pearson χ² test and Fisher exact test were used for nominal variables. Survival rate was calculated and plots constructed by the Kaplan-Meier method and compared between groups with a log-rank test. All statistical analyses were performed using the SPSS computer software package (Version 10.0, Chicago, IL, USA). A P-value < 0.05 was considered statistically significant.

**RESULTS**

**Clinical features**

Table 1 summarizes the demographic features of 23 GIST patients receiving sunitinib. There were 16 male and 7 female patients with a median age of 59 years (range from 24 to 83 years). The stomach was the most common site for GISTs treated with sunitinib (8/23; 35%), followed by the jejunum (5/23; 22%), the ileum (5/23; 22%), and the rectum (3/23; 13%) (Table 1).

**Treatment and outcomes before and after use of sunitinib**

In Taiwan, sunitinib has been approved for treatment of metastatic GIST patients facing IM intolerance or failure since February 2009. Before 2009, sunitinib was administered to selected patients with unresectable or metastatic (advanced) GISTs facing IM failure or intolerance because they were enrolled in clinical trials. Sunitinib (12.5-50 mg/d) was given to 23 patients and all 23 patients were followed after administration of sunitinib at regular intervals until death or until the time of this manuscript writing. The median follow-up time after sunitinib was 7.5 mo, range: 1-25.8 mo. Overall, 2 patients (8.7%) had a complete response (CR), 4 (17.4%) had a partial response (PR), 9 had stationary disease (SD) (39.1%), and 8 had progressive disease (PD) (34.8%). A clinical benefit was observed in 65.2% of GIST patients. Among the 23 patients, the median TTR for 2 patients with CR was 3.75 mo and was 3.67 mo for 4 PR patients. The median TTP was 2.37 mo and the median survival is still unknown in the 8 PD patients (Table 2). During the median 7.5 mo follow-up after sunitinib use, the median PFS and OS of these 23 GIST patients after sunitinib treatment was 8.4 and 14.1 mo, respectively (Figures 1 and 2).

**Spectrum of mutations in 23 advanced GIST patients**

Tumor specimens suitable for genetic analysis were available from 21 (84.4%) of the 23 GIST patients with IM failure or intolerance. Overall, 18 (85.7%) of the 21 examined GISTs had activated mutations of KIT exon 9 and 11. Six of 21 (28.6%) GISTs had exon 9 mutation, 12 (57.1%) had exon 11 mutation, and 1 (4.8%) had no mutation of KIT. One PDGFRα exon 18 mutation was found. One patient had a concurrent deletion mutation in exon 11 and a missense mutation in exon 13; however, the exon 13 mutation was followed by the deletion mutation in exon 11. This patient developed acquired resistance and expired from disease progression. All 6 GISTs had KIT exon 9 mutation and displayed in-frame duplication of nucleotides, resulting in insertion of alanine (A) and tyrosine (Y) at codons 502 and 503. The KIT exon 11 mutations in the 12 GIST patients included insertion and deletion mutations, deletion mutations, and missense mutations.

---

**Table 1** Demographic and genetic data of 23 Taiwanese gastrointestinal stromal tumor patients with imatinib failure or intolerance treated with sunitinib α (%)<ref>

| Genetic spectrum | Local recurrence | Tumor recurrence |
|------------------|------------------|------------------|
| Deletion mutation| Peritoneum        | Liver            |
| Deletion and insertion mutation |Locoregional | Hepatic          |
| Missense mutation |Mesentery        | Rectum           |

**Table 2** Antitumor response of 23 Taiwanese with advanced gastrointestinal stromal tumor treated with sunitinib\textsuperscript{α, β, γ}

| α (%) | Sunitinib duration (median, mo) | TTR/TTP (median, mo) | OS (median, mo) |
|-------|---------------------------------|----------------------|-----------------|
| CR    | 2 (8.7)                         | 9.85                 | 3.75/NA         |
| PR    | 4 (17.4)                        | 12.3                 | 3.67/12.71      |
| SD    | 9 (39.1)                        | 11.9                 | 1.87/13.53      |
| PD    | 8 (34.8)                        | 3.63                 | 2.37/NA         |

CR: Complete response; PR: Partial response; SD: Stationary disease; PD: Progression of disease; TTR: Time to response; TTP: Time to progression; OS: Overall survival.

---

Chen YY et al. Sunitinib for GIST after imatinib failure
In 12 patients with GISTs harboring KIT exon 11 mutations, the clinical benefit rate was 75% (2 CR, 2 PR, and 5 PR) and 3 of 6 patients with tumors containing a KIT exon 9 mutation had a clinical benefit of 50% (1 PR and 2 SD) (not significant, $P = 0.344$) (Table 3). The median PFS and OS for the 12 GIST patients who had KIT exon 11 mutations after sunitinib use was 8.8 mo and still not reached, respectively. The median PFS and OS for the 6 patients with tumors containing a KIT exon 9 mutation were 3.7 and 13.5 mo, respectively. The twelve GIST patients who had KIT exon 11 mutations had similar PFS and OS to that of 6 patients with tumors containing a KIT exon 9 mutation (Figures 3 and 4).

Adverse events in 23 advanced GIST patients receiving sunitinib
Hand-foot syndrome was the most common cause of grade III adverse effects (26.1%), followed by anemia (17.4%), and neutropenia (13.0%). None of 11 patients had hypothyroidism after use of sunitinib (Table 4).

DISCUSSION
We had shown that IM significantly prolongs the post-recurrence and OS of Taiwanese patients with advanced GISTs. However, approximately 50% of GIST patients eventually develop progression in 24 mo after IM treatment and emerge as a challenge. This study confirmed the positive effect of sunitinib on improving PFS.
and OS of advanced GIST patients facing IM failure or intolerance. This study reported a median PFS and OS for 23 advanced GIST patients of 8.4 and 14.1 mo, respectively, after sunitinib administration for a median period of 6.0 mo.

Sunitinib induced a sustained clinical benefit in more than 50% of Taiwanese patients with advanced GISTs (15/23; 65.2%)\[^{[29]}\] in our study, which was better than Henrich’s report. A CR induced by tyrosine kinase inhibitors on GIST patients has been sporadically reported. The US S0033 phase III study revealed that the CR rate was 3% for 751 metastatic or unresectable GIST patients receiving 400 or 800 mg IM daily\[^{[30]}\]. In the EORTC 62005 phase III study, the CR rate was 4.76% for 923 metastatic or unresectable patients receiving 400 or 800 mg imatinib daily\[^{[31]}\]. In contrast to the previous studies, the CR rate in this study was 8.7% (2/23) and the median TTR for 2 patients that had a CR was 3.73 mo. The high incidence of CR in this study, even for patients using the second line tyrosine kinase, is because 1 of these 2 patients underwent surgery to achieve complete tumor removal. The limited experience on CR after sunitinib treatment for advanced or metastatic GIST patients facing IM failure or intolerance may still not justify the use of surgery as an adjunct method for target therapy in selected patients.

Regarding the relationship between response rate and kinase mutation, KIT exon 11 and exon 9 mutations predict a favorable response to IM\[^{[29]}\]. Henrich reported that the clinical activity of sunitinib after IM failure is significantly impacted by both primary and secondary mutations in the predominant pathogenic kinases, which has implications on optimal treatment of patients with GIST. Heinrich reported that both the clinical benefit and the objective response rates with sunitinib were higher in patients with primary KIT exon 9 mutations than with exon 11 mutations. Similarly, PFS and OS were significantly longer in patients with primary KIT exon 9 mutations or a wild-type genotype than in those with KIT exon 11 mutations\[^{[29]}\]. A possible explanation is that the potency of sunitinib against wild-type and exon 9 mutant KIT was superior to that of imatinib in vitro, whereas both drugs exhibited similar potency against KIT exon 11 mutant kinases. These results suggest that the greater clinical benefit seen in sunitinib-treated patients with exon 9 mutant or wild-type imatinib-resistant GISTs may be related to the greater potency of sunitinib against these kinases\[^{[29]}\]. In contrast to Heinrich’s study, the clinical benefit, PFS, and OS did not differ between the groups of patients whose GISTs had KIT exon 9 or exon 11 mutation. Although the KIT oncoproteins encoded by exon 9 and exon 11 mutants were unequally sensitive to sunitinib in vitro\[^{[29]}\], the limited case number and racial difference might partly explain the similar clinical response rate of sunitinib in terms of KIT exon mutations in Taiwanese GIST patients.

Sunitinib was reasonably well tolerated in our study and the most common treatment-related adverse events were fatigue, diarrhea, skin discoloration, and nausea. Treatment-related adverse events of any severity grade were reported in 83% of sunitinib-treated patients, and serious treatment-related adverse events were reported in 20% of patients\[^{[29]}\]. In contrast to western GIST patients, hand-foot syndrome was the most common cause of grade III adverse events in our study. The reason for this discrepant incidence of hand-foot syndrome is still unknown and needs to be fully clarified. Racial differences in drug metabolism or pharmacokinetics are possible reasons for this observation\[^{[32]}\]. However, Lee et al.\[^{[34]}\] reported a higher frequency of hand-foot syndrome in Asian patients at Asian sites compared to Asian patients at non-Asian sites and in non-Asian patients in more than 4000 renal cell carcinoma patients receiving sunitinib. A lower frequency of some GI-related adverse events (AEs) in Asian patients at non-Asian sites compared to frequencies in Asian patients at Asian sites and in non-Asian patients has been observed. Recent evidence suggest that heterogeneity in toxicity and efficacy among patients receiving anti-VEGF therapy can be partially explained by genomic variability, including single-nucleotide polymorphisms, providing a possible explanation for the differences in AE frequencies between Asians and non-Asians in this analysis\[^{[34]}\].

Sunitinib-induced hypothyroidism was reported as a side effect in 12% of GIST patients. No hypothyroidism was noted in our series and primary hypothyroidism is not a common complication of therapeutic drugs. Drugs known to affect thyroid function are lithium, thioamides,

### Table 4 Adverse events and selected laboratory abnormalities

| Variable               | Sunitinib (n = 23) |
|------------------------|--------------------|
|                        | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
| Adverse event          |         |         |         |         |
| Anorexia               | 5       | 1       | 0       | 0       |
| Diarrhea               | 6       | 8       | 0       | 0       |
| Constipation           | 1       | 2       | 0       | 0       |
| Fatigue                | 2       | 2       | 0       | 0       |
| Nausea                 | 0       | 0       | 0       | 0       |
| Mucositis/stomatitis   | 4       | 0       | 0       | 0       |
| Vomiting               | 1       | 0       | 0       | 0       |
| Hypertension           | 4       | 4       | 1       | 0       |
| Hand-foot syndrome     | 1       | 2       | 6       | 0       |
| Rash                   | 1       | 4       | 0       | 0       |
| Skin discoloration     | 5       | 0       | 0       | 1       |
| Fever                  | 2       | 0       | 1       | 0       |
| Laboratory abnormalities|        |         |         |         |
| Leukopenia             | 4       | 6       | 1       | 0       |
| Neutropenia            | 2       | 4       | 3       | 0       |
| Febrile neutropenia    | 0       | 0       | 1       | 1       |
| Anemia                 | 8       | 6       | 4       | 0       |
| Elevated creatinine    | 4       | 4       | 0       | 0       |
| Thrombocytopenia       | 6       | 7       | 0       | 0       |
| AST                    | 7       | 1       | 0       | 0       |
| ALT                    | 4       | 0       | 0       | 0       |
| Total bilirubin        | 3       | 1       | 1       | 0       |
| GFR                    | 3       | 2       | 0       | 0       |
| Hypothyroidism         | 0       | 0       | 0       | 0       |

AST: Aspartate aminotransferase; ALT: Alamine aminotransferase; GFR: Glomerular filtration rate.
amiodarone, and cytokines such as interferon and interleukin-2. The molecular mechanisms of sunitinib-induced hypothyroidism are currently unknown but one possible mechanism by which sunitinib direct affects the thyroid is through the inhibition of VEGFR and/or PDGFR. Recent studies in a mouse model have shown that VEGFR inhibition can induce capillary regression in various organs, including the thyroid. Moreover, the vasculature of the thyroid showed the greatest regression of all organs.[33,36]

In conclusion, sunitinib appears to be a safe and effective treatment for Taiwanese patients with imatinib-resistant/intolerant GIST. Sunitinib induced a sustained clinical benefit in more than 50% of Taiwanese advanced GIST patients, even those facing imatinib failure or intolerance, with a median 8.4 month PFS. ORR, PFS, and OS did not differ between patients whose GISTs had wild type KIT, KIT exon 9 mutation, or KIT exon 11 mutation. However, hand-foot syndrome accounted for the most common cause of grade III adverse event.

ACKNOWLEDGMENTS

We would like to thank Novartis (Taiwan) Co., Ltd. for financial support of genetic analysis.

COMMENTS

Background

The clinical safety and efficacy of both imatinib mesylate (IM) and sunitinib in gastrointestinal stromal tumors (GIST) have primarily been established in Western patients living in the USA or Europe and have not been thoroughly studied in Asian patients. Fifty-six centers in 11 countries participated in the phase III trial of sunitinib in GIST, but only 15 of the 312 patients were of Asian descent (10 and 5 in the sunitinib and placebo groups, respectively).

Research fronts

To clarify the efficacy and safety of sunitinib in management of Taiwanese GIST patients facing IM intolerance or failure. The response of this second line target therapy also correlates with genetic status of the tumor.

Innovations and breakthroughs

Sunitinib appears to be a safe and effective treatment for Taiwanese patients with imatinib-resistant/intolerant GIST. Sunitinib induced a sustained clinical benefit in more than 50% of Taiwanese advanced GIST patients, even those facing imatinib failure or intolerance, with a median 8.4 month progression free survival (PFS). ORR, PFS, and overall survival did not differ between patients whose GISTs had wild type KIT, KIT exon 9 mutation, or KIT exon 11 mutation. However, hand-foot syndrome accounted for the most common cause of grade III adverse event.

Applications

The preliminary report helps to clarify the efficacy and safety of sunitinib in management of Taiwanese GIST patients facing IM intolerance or failure.

Peer review

This is a review of therapeutic effects of sunitinib on 22 Taiwanese patients with metastatic GISTs after IM failure. Their data showed that sunitinib was helpful in 15 of the 23 patients, and the clinical benefits of sunitinib did not differ in patients with either primary KIT exon 9 or exon 11 mutation. Although the finding of this study is not new for sunitinib has been shown effective for IM failure, it is an interesting report showing authors’ experience in using sunitinib in Taiwanese patients.

REFERENCES

1. Lewis JJ, Brennan MF. Soft tissue sarcomas. Curr Probl Surg 1996; 33: 817-872
2. Rossi CR, Mocellin S, Mencarelli R, Foletto M, Pilati P, Nitti D, Lise M. Gastrointestinal stromal tumor: from a surgical to a molecular approach. Int J Cancer 2003; 107: 171-176
3. DeMatteo RP, Lewis JJ, Leung D, Mudan SS, Woodruff JM, Brennan MF. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. Ann Surg 2000; 231: 51-58
4. Kindblom LG, Remotti HE, Aldenberg F, Meis-Kindblom JM. Gastrointestinal pacemaker cell tumor (GIPACT): gastrointestinal stromal tumors show phenotypic characteristics of the interstitial cells of Cajal. Am J Pathol 1998; 152: 1259-1269
5. Hirota S, Isozaki K, Moriyama Y, Hashimoto K, Nishida T, Ishiguro S, Kawano K, Hanada M, Kurata A, Takeda M, Muhammad Tunio G, Matsuzawa Y, Kanakura Y, Shinomura Y, Kitamura Y. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. Science 1998; 279: 577-580
6. Demetri GD, von Mehren M, Blanke CD, Van den Abbeele AD, Eisenberg B, Roberts PJ, Heinrich MC, Tuveson DA, Singer J, Janicek M, Fletcher JA, Silverman SG, Silberman SL, Capdeville R, Kiese B, Peng B, Dimitrijevic S, Druker BJ, Corless C, Fletcher CD, Joensuu H. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med 2002; 347: 472-480
7. Verweij J, Casali PG, Zalberg J, LeCesne A, Reichardt P, Blay JY, Issels R, van Oosterom A, Hogendoorn PC, Van Glabbeke M, Bertulli R, Judson I. Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. Lancet 2004; 364: 1127-1134
8. Yeh CN, Chen TW, Wu TJ, Hsueh S, Jan YY. Treatment of patients with advanced gastrointestinal stromal tumor of small bowel: implications of imatinib mesylate. World J Gastroenter 2006; 12: 3760-3765
9. Yeh CN, Chen TW, Lee HL, Liu YH, Chao TC, Hwang TL, Jan YY, Chen MF. Kinase mutations and imatinib mesylate response for 64 Taiwanese with advanced GIST: preliminary experience from Chang Gung Memorial Hospital. Ann Surg Oncol 2007; 14: 1123-1128
10. Akwari OE, Dozios RR, Weiland LH, Beahrs OH. Leiomyosarcoma of the small and large bowel. Cancer 1978; 42: 1375-1384
11. Shiu MH, Farr GH, Papachristou DN, Najdul SI. Myxosarcomas of the stomach: natural history, prognostic factors and management. Cancer 1982; 49: 177-187
12. McGrath PC, Neifeld JP, Lawrence W Jr, Kay S, Horsley JS 3rd, Parker GA. Gastrointestinal sarcomas. Analysis of prognostic factors. Ann Surg 1987; 206: 708-710
13. Ng EH, Pollock RE, Munsell MF, Atkinson EN, Romsdahl MM. Prognostic factors influencing survival in gastrointestinal leiomyosarcomas. Implications for surgical management and staging. Ann Surg 1992; 215: 68-77
14. Druker BJ, Tamura S, Buchdunger E, Ohno S, Segal GM, Fanning S, Zimmermann J, Lydon NB. Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr-Abl positive cells. Nat Med 1996; 2: 561-566
15. Buchdunger E, Cioffi CL, Law N, Stover D, Ohno-Jones S, Druker BJ, Lydon NB. Abl protein-tyrosine kinase inhibitor STI571 inhibits in vitro signal transduction mediated by c-kit and platelet-derived growth factor receptors. J Pharmacol Exp Ther 2000; 295: 139-145
16. Heinrich MC, Griffith DJ, Druker BJ, Wait CL, Ott KA, Ziegler AJ. Inhibition of c-kit receptor tyrosine kinase activity by STI 571, a selective tyrosine kinase inhibitor. Blood 2000; 96: 925-932
17. Wang WI, Healy ME, Sattler M, Verma S, Lin J, Moulag L, Stiles CD, Griffith JD, Johnson BE, Salgia R. Growth inhibition and modulation of kinase pathways of small cell lung cancer cell lines by the novel tyrosine kinase inhibitor STI 571. Oncogene 2000; 19: 3521-3528
18. Osusky KL, Hallahan DE, Fu A, Ye F, Shyr Y, Geng L. The receptor tyrosine kinase inhibitor SU11248 impedes endo-
thelial cell migration, tube formation, and blood vessel formation in vivo, but has little effect on existing tumor vessels. Angiogenesis 2004; 7: 225-233.

19 Abrams TJ, Lee LB, Murray LJ, Pryer NK, Cherrington JM. SU11248 inhibits Kit and platelet-derived growth factor receptor beta in preclinical models of human small cell lung cancer. Mol Cancer Ther 2003; 2: 471-478.

20 Mendel DB, Laird AD, Xin X, Louie SG, Christensen JG, Li G, Schreck RE, Abrams TJ, Ngai TJ, Lee LB, Murray LJ, Carver J, Chan E, Moss KG, Haznedar JO, Sukbunkhunthong J, Blake RA, Sun L, Tang C, Miller T, Shrizarian S, McMahon G, Cherrington JM. In vivo antitumor activity of SU11248, a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor and platelet-derived growth factor receptors: determination of a pharmacokinetic/pharmacodynamic relationship. Clin Cancer Res 2003; 9: 327-337.

21 Murray LJ, Abrams TJ, Long KR, Ngai TJ, Olson LM, Hong W, Keast PK, Brassard JA, O'Farrell AM, Cherrington JM, Pryer NK. SU11248 inhibits tumor growth and CSF-1R-dependent osteolysis in an experimental breast cancer bone metastasis model. Clin Exp Metastasis 2003; 20: 757-766.

22 O'Farrell AM, Abrams TJ, Yuen HA, Ngai TJ, Louie SG, Yee KW, Wong LM, Hong W, Lee LB, Town A, Smolich BD, Manning WC, Murray LJ, Heinrich MC, Cherrington JM. SU11248 is a novel FLT3 tyrosine kinase inhibitor with potent activity in vitro and in vivo. Blood 2003; 101: 3597-3605.

23 Schuenneman AJ, Himmelfarb E, Geng L, Tan J, Donnelly E, Mendel D, McMahon G, Hallahan DE. SU11248 maintenance therapy prevents tumor regrowth after fractionated irradiation of murine tumor models. Cancer Res 2003; 63: 4009-4016.

24 Demetri GD, van Oosterom AT, Garrett CR, Blackstein ME, Shah MH, Verweij J, McArthur G, Judson IR, Heinrich MC, Morgan JA, Desai J, Fletcher CD, George S, Bello CL, Huang X, Baum CM, Casali PG. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet 2006; 368: 1329-1338.

25 Shirao K, Nishida T, Doi T, Komatsu Y, Muro K, Li Y, Ueda E, Ohtsu A. Phase I/II study of sunitinib malate in Japanese patients with gastrointestinal stromal tumour after failure of prior treatment with imatinib mesylate. Invest New Drugs 2010; 28: 866-875.

26 Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG. 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: 205-216.

27 Cancer Therapy Evaluation Program. Common toxicity criteria (CTC) version 2.0. Bethesda, MD: National Cancer Institute, April 30, 1999. Available from: URL: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctvc20_4-30-992.pdf

28 Heinrich MC, Corless CL, Demetri GD, Blanke CD, von Mehren M, Joensuu H, McGreevey LS, Chen CJ, Van den Abbeele AD, Druker BJ, Kiese B, Eisenberg B, Roberts PJ, Singer S, Fletcher CD, Silberman S, Dimitrijevic S, Fletcher JA. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. J Clin Oncol 2003; 21: 4342-4349.

29 Heinrich MC, Maki RG, Corless CL, Antonescu CR, Harlow A, Griffith D, Town A, McKinley A, Ou WB, Fletcher JA, Fletcher CD, Huang X, Cohen DP, Baum CM, Demetri GD. Primary and secondary kinase genotypes correlate with the biological and clinical activity of sunitinib in imatinib-resistant gastrointestinal stromal tumor. J Clin Oncol 2008; 26: 5352-5359.

30 Blanke CD, Rankin C, Demetri GD, Ryan CW, von Mehren M, Benjamin RS, Raymond AK, Bramwell VH, Baker LH, Maki RG, Tanaka M, Hecht JR, Heinrich MC, Fletcher CD, Crowley JJ, Borden EC. Phase III randomized, intergroup trial assessing imatinib mesylate at two dose levels in patients with unresectable or metastatic gastrointestinal stromal tumours expressing the kit receptor tyrosine kinase: S0033. J Clin Oncol 2008; 26: 626-632.

31 Zalcberg JR, Verweij J, Casali PG, Le Cesne A, Reichardt P, Blay JY, Schlemmer M, Van Glabbeke M, Brown M, Judson IR. Outcome of patients with advanced gastro-intestinal stromal tumours crossing over to a daily imatinib dose of 800 mg after progression on 400 mg. Eur J Cancer 2005; 41: 1751-1757.

32 Miettinen M, Sarlomo-Rikala M, Lasota J. Gastrointestinal stromal tumours: recent advances in understanding of their biology. Hum Pathol 1999; 30: 1213-1220.

33 Anderson R, Jatoi A, Robert C, Wood LS, Keating KN, Lacouture ME. Search for evidence-based approaches for the prevention and palliation of hand-foot skin reaction (HFSR) caused by the multikinase inhibitors (MKIs). Oncologist 2009; 14: 291-302.

34 Lee S, Chung HC, Mainwaring P, Ng C, Chang JW, Kwong P. An Asian subpopulation analysis of the safety and efficacy of sunitinib in metastatic renal cell carcinoma. Eur J Cancer Suppl 2009; 7: 428.

35 Balfett F, Le T, Seminio B, Thurston G, Kuo CJ, Hu-Lowe D, McDonald DM. Cellular changes in normal blood capillaries undergoing regression after inhibition of VEGF signaling. Am J Physiol Heart Circ Physiol 2008; 290: H547-H559.

36 Kamba T, Tam BY, Hashizume H, Haskell A, Sennino B, Mancuso MR, Norberg SM, O'Brien SM, Davis RB, Gowen LC, Anderson RD, Thurston G, John S, Springer ML, Kuo CJ, McDonald DM. VEGF-dependent plasticity of fenestrated capillaries in the normal adult microvasculature. Am J Physiol Heart Circ Physiol 2006; 290: H560-H576.