Background: Imatinib used to be the only effective treatment for advanced gastrointestinal stromal tumor. However, early clinical reports have shown that sunitinib has substantial anti-cancer activity in patients with advanced gastrointestinal stromal tumor after failure of imatinib.

Methods: Eighteen Japanese patients with advanced gastrointestinal stromal tumor who were resistant or intolerant to previous treatment with imatinib were entered into this study. These patients were given sunitinib orally, once daily at a 50-mg starting dose, in 6-week cycles with 4 weeks on and 2 weeks off treatment. Tumor response and drug safety were then evaluated.

Results: Median time-to-treatment failure was 207 days. Overall, 5.6% (1/18) of patients achieved partial response, 38.9% (7/18) had stable disease and 44.4% (8/18) had progressive disease. The common adverse events were hand-foot syndrome, liver dysfunction, fatigue, anorexia and hypertension. Mild anemia, leukocytopenia and neutropenia were also noted. Nine patients required dose reduction or cessation because of adverse events.

Conclusions: This study demonstrates that sunitinib may be an effective agent for advanced gastrointestinal stromal tumor after failure of imatinib in clinical practice.

Key words: gastrointestinal stromal tumor (GIST) – sunitinib – efficacy and safety

INTRODUCTION

Gastrointestinal stromal tumor (GIST) is a form of sarcoma and the most common mesenchymal tumor of the gastrointestinal tract, distinguishable from other soft tissue neoplasms by immunohistochemistry (1). The tumor probably arises from mutations in precursor cells that normally give rise to the interstitial cells of Cajal. Like these cells, most GISTs express the protein product of the KIT proto-oncogene, a transmembrane receptor tyrosine kinase, whose activity would normally be regulated by binding of its ligand. Approximately 85–90% of GISTs demonstrate gain-of-function KIT gene mutations that lead to constitutive activation of KIT kinase (2–4). A much smaller proportion (5%) demonstrates analogous gain-of-function mutations in PDGFRα, the gene encoding platelet-derived growth factor receptor α (PDGFRα); less than 10% contain no identified receptor tyrosine kinase mutations (2–4). Activating mutations of KIT and PDGFRα have been defined as the driving force behind development and maintenance of the malignant phenotype in most cases of GIST. Understanding the molecular pathophysiology of this condition has allowed rational development of agents that target these signaling aberrations in the cancer cell. Imatinib mesylate, a selective inhibitor of the kinase activities of KIT and PDGFRα, has substantially improved clinical outcomes for patients with advanced disease (5–7). However, in a pivotal study of imatinib in advanced GIST, 5% of patients showed primary resistance to imatinib and another 14% developed early resistance (8). Secondary or acquired resistance develops after a median of about 2 years of treatment with imatinib (9). Such resistance can develop through various mechanisms, the most common being secondary KIT mutations in clonally expanded cancer cells (5,10,11). Effective alternative treatments for use after failure of imatinib therapy became an important unmet medical need, justifying the
development of alternative agents. Sunitinib malate is an oral multigene receptor tyrosine kinase inhibitor, which has shown antiangiogenic and antitumor activities in several in vitro and in vivo tumor models (6,7,12–15). Sunitinib inhibits the VEGFR kinases, which are important in tumor-related angiogenesis, a property not shared by imatinib. Results from a phase III study (16) showed that sunitinib had promising clinical activity in patients with imatinib-resistant disease. Although Shirao et al. (17) also reported the efficacy and safety of sunitinib in Japanese patients, there are no Japanese data about the clinical potential of sunitinib in clinical practice. The objectives of this retrospective study were to assess the efficacy and safety of sunitinib in Japanese patients with advanced GIST after failure of imatinib.

PATIENTS AND METHODS

PATIENTS

Eighteen Japanese patients with advanced GIST who were resistant or intolerant to previous treatment with imatinib were recruited to this retrospective study. Inclusion criteria were: pathological evidence of GIST; unidimensionally measurable with computed tomography (CT) or magnetic resonance imaging (MRI); failure of treatment with imatinib, based either on progression of disease according to Response Evaluation Criteria in Solid Tumors [RECIST1.0] (18) or on unacceptably severe toxic effects that precluded further treatment; imatinib last administered at least 2 weeks before starting sunitinib; resolution of all toxic effects of imatinib or other therapy to Grade 1 or less; adequate hepatic, renal and cardiac function; absolute neutrophil count of at least 1500 per microliter; platelet count of at least 100,000 per microliter; and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. The study was approved by the Ethics and Scientific Committee of our institution.

CRITERIA OF EFFICACY AND SAFETY

Tumor responses were assessed by CT or MRI. We used RECIST (19) to determine the best overall response. For patients with multiple metastases, the five largest lesions were followed and measured for response evaluations. Radiographic responses were confirmed by an independent radiologist. Best response was defined as the most complete response achieved by a patient (thus, each patient had a single best response: complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) and the date of best response was the date that response was first detected. The rate of clinical benefit was defined as the proportion of patients who achieved a confirmed objective response (CR or PR) or who had stabilization or no change lasting for at least 24 weeks. These follow-up evaluations were used to determine the duration of response and the date that disease progression was first detected. Patients were assessed for toxicity using the National Cancer Institute Common Toxicity Criteria (NCI-CTC2.0) (20). According to NCI-CTC2.0, each toxicity incident was categorized on a scale of 1–5, with 5 being the most severe.

SUNITINIB TREATMENT

Patients received sunitinib daily for 4 consecutive weeks, followed by a 2-week period without treatment, comprising a 6-week cycle. Sunitinib was given at a starting dose of 50 mg daily; it was given orally in the morning with water and without regard to meals, beginning on day 1 of sunitinib. Treatment was continued until the disease progressed, unacceptable toxic events occurred, or the patient refused to continue. Dose reductions of sunitinib were required in the case of clinically relevant Grade 3 or 4 toxic effects (to 37.5 mg per day and, if additional reduction was warranted, to 25 mg per day), provided that criteria for withdrawal from sunitinib were not met. Dose reduction was also performed if patients were determined to be at the risk of Grade 3 toxic effects. If cardiac toxicity classified as Grade 2 or 3 occurred, we reduced sunitinib to 12.5 mg (1 capsule) per day. However, when patient suffered from symptomatic toxicities of Grade 2 or less, we stopped sunitinib and reduced the dose to 12.5 mg (1 capsule) per day or administration duration of sunitinib like 3 weeks on and 2 weeks off schedule on the next cycle. Patients had regular physical examinations and evaluations of performance status, body weight, complete blood count and serum chemistry. Thyroid function, chest X-ray, electrocardiography and echocardiography were essentially performed every two courses. The administration of each dose and any adverse events were recorded in a diary for each patient.

EVALUATION

The primary endpoint was time-to-treatment failure (TTF). Secondary endpoints included overall confirmed objective response rate as defined using RECIST. Safety and tolerability were assessed by analysis of adverse events, physical examinations, vital signs, electrocardiography, ECOG performance status and laboratory assessments (such as complete blood count with differential count and serum electrolyte measurements). Cardiac function was assessed using electrocardiograms and echocardiography. Severity of adverse events was rated by each investigator using the NCI-CTC.

STATISTICAL ANALYSIS

TTF was defined as the interval between the commencement of and cessation of sunitinib using the Kaplan–Meier method. Statistical analysis was performed using SPSS version 12 (SPSS, Chicago, IL, USA) statistical software.
RESULTS

PATIENT CHARACTERISTICS

From June 2008 to December 2009, 18 patients with malignant GIST were enrolled into the study. In all patients, GIST was diagnosed on the basis of immunohistochemical reactivity to KIT. Patients’ baseline demographic and clinical characteristics are summarized in Table 1. Sixteen (88.9%) patients were resistant and two (11.1%) were intolerant to previous treatment with imatinib. The median patient age was 58.7 years (range, 26–77 years). All patients had a performance status of 0–1, and the most common primary tumor site was the small intestine, including the duodenum. Median total dose of administered sunitinib was 3806 mg and the median number of treatment cycles was 3.5. Median dose intensity of sunitinib was 71.3%. All patients were assessed for response to sunitinib treatment in terms of toxicity and efficacy.

RESPONSE TO TREATMENT

Data on the antitumor response to sunitinib are shown in Table 2. No patients had a CR, PR was observed in 1 patient (5.6%) and SD occurred in 7 patients (38.9%). The patient with PR had a small intestinal GIST of spindle-cell type with liver and peritoneal metastases, and had initially responded to imatinib with PR as assessed by RECIST. After failure with imatinib, this patient was changed to sunitinib. He has had a good response to sunitinib for 15 months (Fig. 1).

Eight patients (44.4%) had PD; these patients showed rapid progression of the disease within 1 month after entry into the study. Two patients (11.1%) were intolerant of sunitinib. After a median follow-up period of 8.0 months (range, 1.8–11.1 months), 15 patients were still alive; the overall median survival time has not yet been reached. Median TTF was 207 days (Fig. 2). Patients who were given a total sunitinib dose $\geq$4000 mg showed a longer TTF (243.8 days) than those receiving a smaller total dose (90.0 days).

ADVERSE EVENTS

The main adverse effects were hand-foot syndrome, liver dysfunction, fatigue, anorexia and hypertension (Table 3). Hand-foot syndrome was observed in 16 patients, liver dysfunction in 16, fatigue in 12, anorexia in 9 and hypertension in 8. Mild anemia, leukocytopenia and neutropenia were also noted (Table 4). Nine patients required dose reduction or drug cessation because of adverse events. Hyperammonemia was observed in one patient, who was given seven courses of sunitinib.

CASE OF HYPERAMMONEMIA

The patient, who was a 56-year-old man, attended our hospital irregularly because his wife noted the developed somnolence during seven courses of sunitinib treatment. He presented with a flapping tremor and smell of ammonia. He had no past history of liver disorder or viral hepatitis. Investigations revealed an increased serum level of ammonia, which was irreversible after 2 months’ discontinuation of sunitinib. Celiac and superior mesenteric artery angiography was performed to examine the cause of hyperammonemia; CT with arterial portography showed a portovenous shunt (Fig. 3).

DISCUSSION

Based on TTF and tumor response, sunitinib demonstrated similar efficacy to that previously reported in a phase III trial involving predominantly western patients with failure of imatinib (16) and in a Japanese phase I/II trial (17). The present TTF was 207 days (29.6 weeks), while time to
progression (TTP) in the above-mentioned phase III and phase I/II trials was 27.3 and 27.9 weeks, respectively. The present study was retrospective, and the date of disease progression could not be determined because of the lack of radiological examinations. We were not able to compare TTF with TTP directly, but these durations are considered to show a similar tendency. In the current study, 5.6% of patients showed objective response (CR + PR) and 44.5% demonstrated clinical benefit response (CR + PR + SD). On the other hand, objective response and clinical benefit response of the phase III study were 7 and 24%, and those of the Japanese phase I/II study were 13 and 40%, respectively. The benefit of sunitinib in clinical practice is very important because sunitinib is the only drug approved for second-line treatment of imatinib-resistant/intolerant GIST.

Toxicities of sunitinib, which were predominantly mild to moderate, were manageable and reversible. Fatigue was the most common adverse event in the phase III trial, but hand-foot syndrome was the most common adverse event in the present study, as in the Japanese phase I/II trial. The difference in the incidences of toxicities may be caused by racial differences, as well as by the small number of patients and insufficient follow-up period in the present study. Long-term follow-up of these patients will be important to fully define the tolerability of multitargeted kinase inhibition. In the Japanese phase I/II trial, the incidence of severe adverse events was 25%. In the present study, although two severe adverse events (11.1%) associated with sunitinib led to treatment discontinuation, these were reversible through dose interruption and standard supportive medical treatment.

Hand-foot syndrome was generally observed 2 weeks after the start of sunitinib. If this syndrome occurs within 1 week and is categorized as Grade 2, we suspend sunitinib therapy. The next course is then started at a reduced dose (12.5 mg; a one-capsule reduction). Although this reduces the dose intensity of sunitinib, it allows a long duration of therapy. In fact,
median dose intensity of sunitinib was 71.3% and TTF was long at 29.6 weeks, similar to the TTP of the Japanese phase I/II study. Long-term administration should be the first priority of sunitinib treatment. However, in the present study, the follow-up period and number of patients given sunitinib were inadequate to provide direct evidence that it can prolong survival. Hence, we consider that the most important purpose of sunitinib treatment is to maintain previous activities of daily living. Maximum efficacy of antitumor therapy relates to sufficient dose and time. Sunitinib is a well-tolerated medication but has slightly greater toxicity than first-line imatinib. Therefore, we emphasized medication duration rather than dose of sunitinib, but despite this strategy, dose intensity was adequate (median relative dose intensity: 71.3%) and TTF was satisfactory at 29.6 weeks.

It is very important to manage symptomatic as well as non-symptomatic toxicities. Although the incidence of hyperammonemia is reported to be very low, we encountered one case. This adverse event may in part be caused by a vascular disorder related to the antiangiogenic properties of sunitinib. Sunitinib is multitargeted agent and might cause different toxicities from conventional cytotoxic agents. Although common toxicities have been reported by the global phase III trial and Japanese phase I/II trial, rare toxicities are not well demonstrated in such clinical trials and further data collection is therefore essential for the appropriate management of sunitinib. We intend to focus on the best management of toxicities so that long-term exposure and high dose intensity of sunitinib are acquired. Further investigations should be considered to maximize the benefits of sunitinib in patients with GIST.

Conflicts of interest statement
None declared.

References
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Figure 3. Computed tomography with arterial portography. Six consecutive images of computed tomography show the well-enhanced hepatic vein and clearly reveal the connection between the portal vein (P7) and right hepatic vein (see arrow heads on images).


