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Fractioned Dose Regimen of Sunitinib for Patients with Gastrointestinal Stromal Tumor: A Pharmacokinetic and Treatment Efficacy Study[1]

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Abstract

AIM: Sunitinib has shown benefit in patients with imatinib (IM)–resistant gastrointestinal stromal tumor (GIST). However, its advantages are somewhat diminished because of associated toxicities. Herein, we clarify the efficacy and safety of fractioned dose regimen of sunitinib by a pharmacokinetic and efficacy study. *MATERIALS AND METHODS:* Between 2001 and March 2013, a total of 214 patients with metastatic GIST was treated at Chang Gung Memorial Hospital. Among them, 55 (11.6%) patients who received sunitinib were investigated. One group of patients was administered with standard dose of once-daily sunitinib (standard dose group) and the other group was administered with standard total daily dose of sunitinib in fractioned doses (fractioned dose group). *RESULTS:* Thirty-two male and 23 female patients with a median age of 55 years received sunitinib. The median duration of sunitinib administration was 9.2 months. The clinical benefit was 65.2%. The mean peak blood level of sunitinib in patients with fractioned doses was significantly lower than that in those with once-daily dose (83.4 *vs* 50.1 ng/ml, $P = .01$). The rates of adverse effects of hand-foot syndrome, mucositis, and yellow skin were significantly decreased by fractioned doses of sunitinib. However, the progression-free and overall survival did not differ between patients with different treatment regimens. *CONCLUSION:* The fractioned dose regimen of sunitinib appears to be a safe and effective treatment for patients with IM-resistant/intolerant GISTs. Significantly decreased toxicity of this regimen could be explained by significantly lower peak sunitinib blood level. However, the treatment efficacy is not reduced by this regimen.

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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 [1], they account for the most common mesenchymal malignancy of the GI tract [2]. GISTs appear to be related to the interstitial cells of Cajal [3] 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 [4,5]. The KIT tyrosine kinase inhibitor imatinib (IM) mesylate has shown a promising clinical result for patients with advanced GIST [6], and several trials have shown a promising effect of this targeted therapy [6,7]. Our previous study showed that IM mesylate significantly affected survival in patients with GIST [8–10]. However, progression of GIST eventually develops and emerges as a challenge.

Sunitinib is a multitargeted tyrosine kinase inhibitor that predominantly targets vascular endothelial growth factor receptors and is used for treatment of metastatic renal cell carcinoma and GIST [11]. In addition to vascular endothelial growth factor receptors, sunitinib inhibits other receptor tyrosine kinases, including platelet-derived growth factor receptors (PDGFRs), KIT, Fms-like tyrosine kinase-3, colony-stimulating factor 1, and RET, which are involved in a great variety of malignancies [12]. In GIST, sunitinib is administered as a second-line targeted therapy, offering a new treatment option for patients who are refractory to IM. Although continuous once-daily dosing of sunitinib appears to be a safe and effective dosing regimen for patients with IM-resistant GIST, several adverse events (AEs), such as diarrhea, cutaneous toxicity, hypertension, myelosuppression, and thyroid dysfunction, have been reported [12]. These drug-related toxicities may reduce the treatment duration and patient compliance and therefore diminish treatment advantages of sunitinib. In this study, we investigated the efficacy, safety, and pharmacokinetics (PK) of administering the total daily dose of sunitinib in fractioned doses when treating GIST patients with IM intolerance or failure. The goal was to treat GIST patients with a regimen that has similar efficacy and a better safety profile.

Methods

Patient Population

Between 2001 and March 2013, a total of 214 patients who had histologically confirmed, recurrent, or metastatic GIST that expressed CD117 or CD34 was treated at the Department of Medical Oncology and Surgery in Chang Gung Memorial Hospital in Taiwan. Failure of prior IM therapy, demonstrated by disease progression (based on Response Evaluation Criteria in Solid Tumors) [13] or discontinuation of IM due to toxicity, was one of the inclusion criteria in this study. Additional eligibility criteria included an Eastern Cooperative Oncology Group performance status of 0 or 1 and adequate cardiac, hepatic, renal, coagulation, and hematologic functions. Key exclusion criteria included lack of recovery from the acute toxic effects of previous anticancer therapy or IM treatment, discontinuation of IM therapy within 2 weeks or of any other approved/investigational drugs for GIST within 4 weeks before starting sunitinib treatment, clinically significant cardiovascular events or diseases in the previous 12 months, diabetes mellitus with clinical evidences 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 weeks 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 (101-0274C), and a written informed consent for drug administration and the analysis of tumor-associated genetic alteration was obtained independently from each patient.

Study Design and Evaluation of Efficacy and Safety

A retrospective study was conducted to evaluate the effects of sunitinib in inducing objective responses in Taiwanese GIST patients. Patients received 50 mg interruptedly (4 weeks on and 2 weeks off) or 37.5 mg continuously of sunitinib in 12.5-mg capsules taken daily through mouth with food. We classified them into two groups as follows: one group of patients was administered with the above regimens once daily (standard dose group, i.e., four capsules (12.5 mg per capsule) per day, 4 weeks on and 2 weeks off, or three capsules continuously), and the other group of patients was administered with the above regimens in fractioned doses (fractioned dose group, i.e., one capsule (12.5 mg per capsule) four times per day, 4 weeks on and 2 weeks off, or one capsule three times a day continuously without rest).

The patients received regular physical examinations and evaluations of performance status, body weight, complete blood counts, and serum chemistries. The administration of each dose and any AEs were recorded for each patient. Standard computed tomography was performed on each patient every 3 months in the first 3 years and every 6 months for the following 2 years to assess patients' responses.

Measurement of efficacy was based on objective tumor assessments using Response Evaluation Criteria in Solid Tumors with a minor modification to allow use of standard radiographic protocols for spiral computed tomography. Time to response was defined as the interval from the start of sunitinib treatment to the date of achieving an objective response (complete response or partial response). Time to progression was defined as the interval from the start of sunitinib treatment to the date of reaching disease progression. Progression-free survival (PFS) was defined as the duration of time between sunitinib initiation and tumor progression or death from any causes. Overall survival (OS) was defined as survival after administration of sunitinib, and death was the endpoint of the study. Response rate, PFS, OS, time to response, duration of response, and time to progression were recorded. Safety and tolerability were assessed by analysis of AEs, physical examinations, vital signs, Eastern Cooperative Oncology Group performance status, and abnormal laboratory values (for example, complete blood count with differential, serum electrolyte measurements, and electrocardiogram). Cardiac function was assessed at screening, at day 28 of all treatment cycles, and at the end of treatment with a 12-lead electrocardiogram and multigated acquisition scans. Toxic effects were recorded in accordance with the National Cancer Institute Common Toxicity Criteria [14].

PK Analysis of Sunitinib

Blood samples were collected from selected patients in the study for PK analysis of sunitinib. The blood samples were collected 5 to 6 hours after drug administration to measure the peak levels of sunitinib. Each 8-ml blood sample was collected into heparinized polypropylene tubes, centrifuged at 1000*g* for 10 minutes for plasma