

研究成果の刊行に関する一覧表

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厚生労働科学研究費補助金

がん臨床研究事業

限局型小細胞肺癌に対する新たな標準的治療の確立に関する研究

研究成果の刊行物・別刷

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|-------|-------|----------------------|
| 研究代表者 | 田村 友秀 | 国立がん研究センター中央病院 |
| 研究分担者 | 大江裕一郎 | 国立がん研究センター東病院 |
| | 森 清志 | 栃木県立がんセンター |
| | 岡本 浩明 | 横浜市立市民病院 |
| | 横山 晶 | 新潟県立がんセンター新潟病院 |
| | 樋田 豊明 | 愛知県がんセンター中央病院 |
| | 里内美弥子 | 兵庫県立がんセンター |
| | 今村 文生 | 大阪府立成人病センター |
| | 平島 智徳 | 大阪府立呼吸器・アレルギー医療センター |
| | 中川 和彦 | 近畿大学医学部 |
| | 安宅 信二 | 近畿中央胸部疾患センター臨床研究センター |
| | 木浦 勝行 | 岡山大学大学院医歯薬学総合研究科 |
| | 山本 信之 | 静岡県立静岡がんセンター |
| | 西尾 誠人 | 癌研究会有明病院 |
| | 武田 晃司 | 大阪市立総合医療センター |
| | 野田 和正 | 神奈川県立がんセンター |

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Phase I and pharmacokinetic study of TSU-68, a novel multiple receptor tyrosine kinase inhibitor, by twice daily oral administration between meals in patients with advanced solid tumors

Yutaka Ueda · Tatsu Shimoyama ·
Haruyasu Murakami · Noboru Yamamoto ·
Yasuhide Yamada · Hitoshi Arioka · Tomohide Tamura

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Abstract

Purpose A single-agent dose-escalating phase I and pharmacokinetic study on TSU-68, a novel multiple receptor tyrosine kinase inhibitor, was performed to determine the safety profile, maximum-tolerated dose for Japanese patients with advanced solid tumors and to define the recommended dose of phase II studies.

Methods Study design was a dose escalation method on a three-patient cohort. TSU-68 was given orally twice daily (bid) between meals without interruption; the estimation of dose escalation was based on the toxicity within 4 week administration at each dose level.

Results Fifteen patients were enrolled into the study. Dose levels studied were 200, 400, 800, and 1,200 mg/m² bid. Grade 3 arrhythmia and anemia/thrombocytopenia were observed in 1 patient each at 800 mg/m² bid. Three patients discontinued continuous oral administration for 4 weeks at 400 and 800 mg/m² bid. At 1,200 mg/m² bid, 2 patients discontinued the treatment over 4 weeks for intolerable fatigue and abdominal pain, respectively. No serious drug-related toxicities have been observed. Grade 1–2 toxicity included urinary/feces discoloration, diarrhea, fatigue, anorexia, abdominal/chest pain, and edema. Tumor shrinkage was observed in 1 patient of NSCLC. In the pharmacokinetics, at any dose levels, C_{max} and AUC_{0–t} after repeated administration of TSU-68 on days 8 and 29 were ~2-fold lower than those after the first administration on day 1; these parameters are similar between days 8 and 28. In addition, no obvious dose-dependent increase in plasma exposure to TSU-68 repeatedly administered was observed over the four dose levels, including the higher dose levels.

Conclusions The tolerable dose in this administration schedule for continuing treatment is thought to be 800 mg/m² or less bid.

Y. Ueda · T. Shimoyama · H. Murakami · N. Yamamoto ·
Y. Yamada · T. Tamura (✉)
Division of Medical Oncology,
National Cancer Center Hospital, 5-1-1, Tsukiji,
Chuo-ku, Tokyo 104-0045, Japan
e-mail: ttamura@ncc.go.jp

H. Arioka
Department of Medical Oncology,
Yokohama Rosai Hospital,
Yokohama, Kanagawa, Japan

Y. Ueda
Department of Internal Medicine,
Kagawa Prefectural Central Hospital, Takamatsu,
Kagawa, Japan

T. Shimoyama
Department of Chemotherapy,
Tokyo Metropolitan Cancer and Infectious Diseases
Center Komagome Hospital, Tokyo, Japan

H. Murakami
Thoracic Oncology Division,
Shizuoka Cancer Center, Shizuoka, Japan

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Introduction

Angiogenesis, the growth of new blood vessels from existing host vasculature, plays a central role in a variety of physiologic and pathologic states. Several families of RTKs such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF) receptors have been implicated in this process and

are involved in diverse developmental and oncogenic processes. VEGF has been shown to be the central positive regulator of tumor angiogenesis, since it is reported that the production of VEGF may be increased in many solid tumors and the ability of production may be correlated with the number of blood vessels and prognosis in breast cancer, stomach cancer, colon cancer, lung cancer, and others [1–4]. VEGF signaling is an attractive therapeutic target, and the antibodies and inhibitors specifically directed against VEGF and/or its receptor VEGFR2 have been demonstrated to potentially prevent vasculature and the growth of a large number of experimental tumor types [5, 6]. FGF and PDGF also play critical roles in angiogenesis, sometimes in concert with VEGF. The prototype FGF family member, FGF2, is a potent mitogen of different cell types including vascular endothelial cells, fibroblasts, and tumor cells, along with its receptors, in a variety of human tumor types [7, 8]. Additionally, FGF2 has been reported to be synergistic with VEGF and to induce the expression of VEGF [9]. FGF is one of the alternative angiogenesis factors during the resistance of VEGF-targeting therapy. PDGF and its receptors have been detected in diverse human cancers, and PDGFRs are expressed on tumor neovasculature and up-regulated during tumor progression [10, 11]. PDGF stimulates angiogenesis by up-regulating VEGF production and modulating the proliferation of pericytes and fibroblast-like cells surrounding the endothelium [12, 13]. Circulating PDGF has been associated with metastases and higher microvessel counts [14, 15].

The signaling cascades generated by these three ligands and their respective receptors are complex, directly and indirectly affecting tumor angiogenesis and tumor growth. In light of the important role of VEGF, FGF, and PDGF and their receptors in tumor angiogenesis and in survival of existing endothelial cells, it is reasonable to expect that simultaneously antagonizing the VEGF, FGF, and PDGF signaling pathways may be more effective than antagonizing one signal transduction alone. TSU-68 is a novel small molecule that competitively inhibits the tyrosine kinase of the receptors for VEGF, basic FGF, and PDGF. TSU-68 has significant antitumor activity against many types of tumor xenograft explants in athymic mice [16]. TSU-68 inhibits angiogenesis through several mechanisms, including the induction of apoptosis in vascular endothelial cells and tumor cells, resulting in perturbing existing tumor vascular function and also inhibiting newly synthesis angiogenesis for the tumor growth [17].

On the basis of these preclinical antiangiogenic and anti-tumor data, we planned a phase I study of TSU-68 in patients with advanced solid tumors using a continuous twice daily between meals oral administration regimen.

Patients and methods

Study population

Patients with a cytologically or histologically confirmed diagnosis of a solid tumor refractory to standard treatment or for whom no standard therapy was available were eligible for this study. Patients with symptomatic brain metastases were excluded. Further eligibility criteria included the following: age ≥ 20 years and ≤ 75 years; World Health Organization performance status of ≤ 2 ; life expectancy of ≥ 60 days; no anticancer therapy in the previous 4 weeks; no serious complication (ileus, myocardial infarction, lung fibrosis, and so on); no past history of thrombosis; adequate function of bone marrow (hemoglobin ≥ 8.0 mg/dl, absolute white blood cell count $\geq 4,000/\text{mm}^3$ or neutrophil count $\geq 2,000/\text{mm}^3$, and white blood cell count $\leq 12,000/\text{mm}^3$); liver (bilirubin ≤ 1.5 mg/dl; AST and ALT ≤ 100 IU/ml); renal (creatinine clearance ≥ 50 ml/min); lung ($\text{PaO}_2 \geq 65$ mmHg); and ability to take oral medication. Local ethics boards approved the protocol and informed-consent brochures in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. All patients gave written informed consent at study entry.

Study design

This study was an open, non-randomized, non-comparative, dose-escalation method on three-patient cohort to adult patients with advanced solid tumors. The trial was designed to comply with the ethical principals of Good Clinical Practice in accordance with the Declaration of Helsinki.

The estimation of dose escalation was based on the toxicity within 4 week administration at each dose level. If no grade 2 toxicity was observed at the previous dose level, a 100% dosage increment was allowed, and if no dose-limiting toxicity (DLT) was observed, a 40% dosage increment was allowed. However, if DLT was observed, a 33% dosage increment was allowed. At each dose level, the third patient was required to have 14 days of treatment before escalation was allowed. Once DLT was seen in one patient at a given dose level, an additional 3 patients had to be treated at that dose level before further dose escalation was allowed. DLT was defined as drug-related adverse events according to National Cancer Institute-Common Toxicity Criteria version 2.0 (NCI-CTC) [18] and comprised any grade 3/4 non-hematologic toxicity and grade 4 hematologic toxicity. The maximum-tolerated dose (MTD) was defined as the dose that induced DLTs in more than 33% of patients during 4 weeks. No intra-patient dose escalation was allowed.

Drug administration

TSU-68, (Z)-3-[2,4-dimethyl-5-(2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-1H-pyrrol-3-yl]-propionic acid was obtained from Taiho Pharmaceutical Co., Ltd. The starting dosing (200 mg/m² twice daily) of Japanese patients was calculated based on the safety results of 4 week toxicology studies in rats and referred to the precedence phase I study of Caucasian patients. At the first day of treatment, patients were given a single dose for pharmacokinetic purposes. The tablet was swallowed immediately more than 2 h after breakfast and supper. Patients were instructed to record their daily amount of tablets taken, the timing in relation to their meals. TSU-68 was taken for 28 consecutive days and was continued in case of stable disease or disease remission after this period for as long as no disease progression and/or no unacceptable drug-related toxicity were seen. Routine antiemetics were not prescribed. TSU-68 administration was immediately interrupted at the occurrence of DLT.

Patient assessment and follow-up treatment

Before therapy, a complete medical history was taken and a physical examination was performed. A complete blood count, including WBC differential, and serum chemistry, including sodium, potassium, chloride, calcium, urea, creatinine, protein, albumin, bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma-glutamyl transpeptidase, and lactate dehydrogenase, were performed, as were urine analysis, Electrocardiogram, and Chest X-ray. In addition, tumor markers related to the tumor type were measured. Weekly evaluations included history, physical examination, a toxicity assessment according to NCI-CTC, complete blood count, serum chemistries, and urine analysis. Tumor measurements were performed before treatment, at 4 weeks, and were evaluated according to the Japan Society for Cancer Therapy criteria [19], which was established based on World Health Organization (WHO) criteria. The criteria for the evaluation of antitumor effects were as follows: complete response (CR), eradication of all cancers and maintenance of the condition for 4 weeks or more; partial response (PR), 50% or more reduction in size of lesions and maintenance of the condition for 4 weeks or more; no change (NC), less than 50% reduction in size of lesions or enlargement of lesions within 25% and maintenance of the condition for 4 weeks or more; progressive disease (PD), 25% or more enlargement of lesions or appearance of new lesions. In case of progressive disease, patients were taken off the study.

Pharmacokinetic and biomarker sampling

For the pharmacokinetic evaluation, TSU-68 was administered once a day on days 1 and 29 and twice a daily during

days 2–28. Blood samples were collected within about 30 min before dosing and at 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, and 12 h after dosing on days 1, 8 and 29. Regarding days 1 and 29, blood samples were also collected at 24 h after dosing. These samples were immediately centrifuged at 3,000 rpm for 10 min at 4°C, after which obtained plasma samples were frozen at –20°C until analysis. Urine samples were collected at the following intervals for measurement of TSU-68: before dosing on day 1, 0–12 and 12–24 h after dosing on days 1 and 29 and 0–12 h after the 1st dosing on day 8. In addition, angiogenesis-related factors such as plasma VEGF, E-selectin, tissue-type plasminogen activator (tPA), vascular cell adhesion molecule-1 (VCAM-1), plasminogen activator inhibitor-1 (PAI-1), and urine VEGF were measured on days 1, 8, and 29.

Pharmacokinetic and biomarker analyses

The pharmacokinetic samples were measured by MDS Pharma Services (Montreal, Canada), and biomarker samples were measured by SRL, Inc. (Tokyo, Japan). TSU-68 concentration was determined using a validated high-performance liquid chromatography method with UV detection, with a lower limit of quantification of 0.1 µg/mL. Non-compartmental pharmacokinetic parameters including area under the plasma concentration–time curves (AUC) from time 0 to the last measurable time (AUC_{0–t}), maximum concentration (C_{max}), time to maximum concentration (T_{max}), and elimination half-life (T_{1/2}) were calculated using PhAST (Ver.2.3, MDS Pharma Services, Montreal, Canada).

Statistical analysis

A regression approach was applied to evaluate dose proportionality in pharmacokinetic parameters. Variability in pharmacokinetics between administration days was evaluated by either the paired Student's *t*-test or an analysis of variance. Statistical significance was considered to be reached at *P* < 0.05. The analysis was performed using the SAS®.

Results

Patient characteristics

Fifteen patients were enrolled in this study between November 2000 and June 2001. All patients were Japanese. Details of dosage level were 3 patients at 200 mg/m² bid, 3 patients at 400 mg/m² bid, 6 patients at 800 mg/m² bid, and 3 patients at 1,200 mg/m² bid. Patient characteristics are listed in Table 1. There were 5 men and 10 women with a

Table 1 Patients characteristics

| Characteristic | Patients number (%) (15 patients) | |
|--------------------|--------------------------------------|------|
| Gender | | |
| Male | 5 | (33) |
| Female | 10 | (67) |
| Age (Years) | | |
| Median | 52.0 | |
| Range | 27–64 | |
| Performance status | | |
| 0 | 1 | (7) |
| 1 | 14 | (93) |
| 2 | 0 | (0) |
| Tumor type | | |
| NSCLC | 6 | (40) |
| Colorectal | 3 | (20) |
| Thymoma | 2 | (13) |
| Others* | 4 | (27) |

* Including cervical cancer, retroperitoneal cancer, intestinal cancer and sarcoma of uterus

median age of 52 years (range, 27–64 years). All patients were evaluated for safety and pharmacokinetic analyses. Three patients discontinued continuous oral administration for 4 weeks due to adverse events (one patient at 800 mg/m²) and disease progress (two patients at 400 mg/m² and 800 mg/m²). In addition, five patients continued the medication after 4 weeks, and these included two patients of dose reduction from 1,200 mg/m² to 800 mg/m².

Dose escalation and maximum-tolerated dose

The dosage was increased from 200 to 400, 800, and 1,200 mg/m² bid by cohort of three patients. At a dosage level of 1,200 mg/m² bid, two patients discontinued the treatment over 4 weeks for intolerable grade 2 fatigue or grade 2 abdominal pain, which were not critical in evaluating the dose escalation for 4 weeks. These two patients of grade 2 toxicities could continue drug administration for 4 weeks (one cycle); however, both patients had to reduce the dosage level to 800 mg/m² bid from the next cycle, and 1,200 mg/m² bid demonstrated unacceptable adverse events for an antitumor drug that is used by long-term consecutive oral administration. On the basis of the results of the pharmacokinetic data, increase in the dosage was terminated, and the three additional patients were administered at a lower dosage of 800 mg/m² bid. At a dosage level of 800 mg/m² bid, one patient was confirmed DLT into a total of six patients. In addition, two patients at 1,200 mg/m² could continue TSU-68 administration with a reduction to 800 mg/m² after 4 weeks. Thus, protocol-defined MTD was

1,200 mg/m² bid, and the acceptable dosage level was estimated 800 mg/m² bid in daily administration.

Dose-limiting toxicity and safety profile

There was one protocol-defined DLT as grade 3 arrhythmia at the dosage level of 800 mg/m² bid. The patient had a complication with supraventricular arrhythmia but had already been controlled by continuous administration of an antiarrhythmic agent. No other DLTs were recorded.

The major drug-related adverse events for 4 week administration with highest grade pre-event per patient are listed in Table 2. Main toxicities of subjective and objective symptom were diarrhea, fatigue, anorexia, nausea, and vomiting. At lower doses, these symptoms were usually mild and required no specific treatment. Six patients experienced grade 1/2 tumor pain in diverse pain events. Edema and/or pleural effusion progression were seen in 7 patients. In addition, other toxicities consisted of grade 1 urinary/feces discoloration based on drug color (such as saffron yellow).

Drug-related abnormal changes in laboratory values were observed in grade 3 anemia and thrombocytopenia from day 27 in one patient at 800 mg/m² bid. Other toxicities experienced in laboratory values were grade 1/2 hypoalbuminemia, grade 1 alkaline phosphatase elevation, and transient grade 1 transaminase elevation.

Four episodes of atrial rhythm abnormalities (atrial fibrillation in a patient and sinus tachycardia in 3 patients with previous cardiac history) were seen. Each patient at 200 mg/m² or 1,200 mg/m² experienced grade 2 supraventricular arrhythmia or grade 1 arrhythmia; these events were of a transient manner, and there was no relationship to TSU-68. One patient of grade 3 supraventricular arrhythmia at 800 mg/m² and one patient of grade 2 atrial fibrillation and grade 1 sinus tachycardia at 1,200 mg/m² were treated with medication, and there was a relationship to TSU-68. One patient of grade 3 supraventricular arrhythmia (DLT) with sinus tachycardia (heart rate over 160/min) occurred on day 6, although this patient had taken verapamil for a long time. TSU-68 treatment was discontinued, and he was treated with digoxin in addition to verapamil dose-up. Subsequently, heart rate was decreased to about 80/min.

Pharmacokinetics

Pharmacokinetic studies were performed in 15 patients at doses from 200 to 1,200 mg/m². The mean concentration–time profiles in each dosage are shown in Fig. 1. Pharmacokinetic results are presented in Table 3. The relationship between the dose and mean C_{max} or AUC_{0–t} is plotted in Fig. 2. After the first dose, the plasma concentration of

Table 2 Number of patients with drug-related adverse events for 28-days administration (highest grads per event per patients)

| Adverse events | 200 mg/m ² bid (N = 3) | | | 400 mg/m ² bid (N = 3) | | | 800 mg/m ² bid (N = 6) | | | 1,200 mg/m ² bid (N = 3) | | | Total* (N = 15) | | Total** (N = 5) | |
|------------------------------------|--------------------------------------|----|----|--------------------------------------|----|----|--------------------------------------|----|----|--|----|----|--------------------|-------|--------------------|-------|
| | G1 | G2 | G3 | G1 | G2 | G3 | G1 | G2 | G3 | G1 | G2 | G3 | N | (%) | N | (%) |
| Urine discoloration | 3 | - | - | 3 | - | - | 6 | - | - | 3 | - | - | 15 | (100) | 5 | (100) |
| Diarrhea | 3 | - | - | 1 | - | - | 2 | 2 | - | 1 | 1 | - | 10 | (67) | 3 | (60) |
| Feces discolored | - | - | - | 1 | - | - | 6 | - | - | 3 | - | - | 10 | (67) | 4 | (80) |
| Fatigue | 1 | - | - | 1 | - | - | 3 | 1 | - | 2 | 1 | - | 9 | (60) | 4 | (80) |
| Anorexia | - | - | - | - | - | - | 3 | 1 | - | 2 | 1 | - | 7 | (47) | 1 | (20) |
| Abdominal pain | - | - | - | - | - | - | 2 | 1 | - | 1 | 1 | - | 5 | (33) | 1 | (20) |
| Face edema | 1 | - | - | 1 | - | - | 1 | - | - | 2 | - | - | 5 | (33) | 3 | (60) |
| Nausea | 1 | - | - | - | - | - | 2 | - | - | - | 1 | - | 4 | (27) | 1 | (20) |
| Upper abdominal pain | 1 | - | - | - | 1 | - | - | - | - | 2 | - | - | 4 | (27) | - | - |
| Chest pain | - | 1 | - | 1 | - | - | - | - | - | 1 | - | - | 3 | (20) | 2 | (40) |
| Vomiting | - | - | - | - | - | - | 2 | - | - | - | 1 | - | 3 | (20) | 1 | (20) |
| Alkaline phosphatase increased | 1 | - | - | 1 | - | - | 3 | - | - | 1 | - | - | 6 | (40) | 2 | (40) |
| Albumin decreased | - | - | - | - | 1 | - | 4 | - | - | - | 1 | - | 6 | (40) | - | - |
| Alanine aminotransferase increased | 1 | - | - | - | - | - | 2 | - | - | - | - | - | 3 | (20) | 3 | (60) |
| Total protein decreased | - | - | - | - | - | - | 3 | - | - | - | - | - | 3 | (20) | - | - |
| Arrhythmia | - | - | - | - | - | - | - | - | 1 | - | - | - | 1 | (7) | 1 | (20) |
| Anemia | - | - | - | - | - | - | - | - | 1 | - | - | - | 1 | (7) | - | - |
| Thrombocytopenia | - | - | - | - | - | - | - | - | 1 | - | - | - | 1 | (7) | - | - |

G common toxicity criteria grade 1 is mild, a grade 2 is moderate, and grade 3 is severe

* The advanced events listed here were reported in >20% of patients and the grade 3 events of patient

** Number of patients with drug-related adverse events after 28 days (200 mg/m² bid; N = 1,400 mg/m² bid; N = 1,800 mg/m² bid; N = 3)

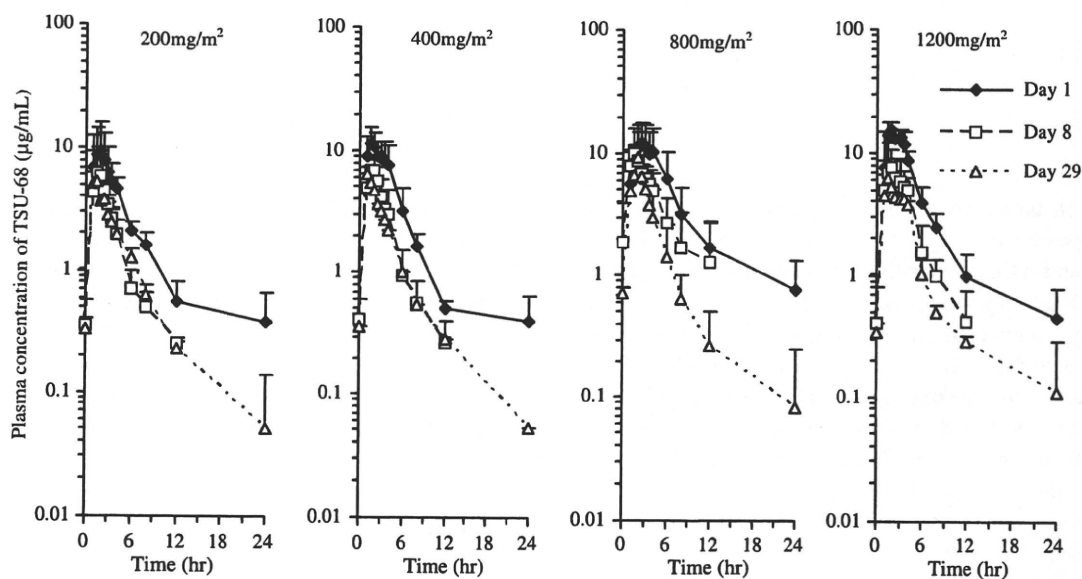
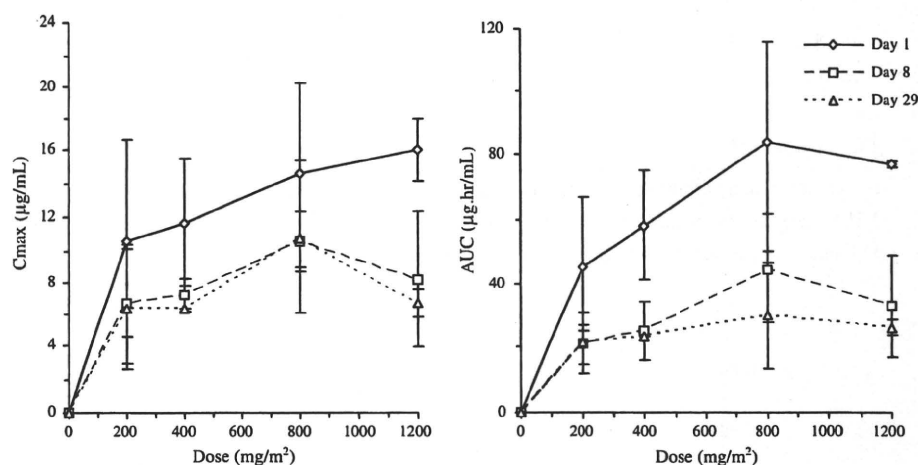


Fig. 1 Plasma concentration-versus-time profile of TSU-68

Table 3 Pharmacokinetic parameters of TSU-68 after day 1, day 8, or day 29 administration

| PK Parameter | Dose (mg/m ²) | Pts. no. | Day 1 | Day 8 | Day 29 |
|------------------------------|---------------------------|----------|----------------|------------------|-------------------|
| T _{max} (h) | 200 | 3 | 2.3 ± 1.5 | 1.7 ± 0.3 | 1.7 ± 0.8 |
| | 400 | 3 | 2.5 ± 1.3 | 1.8 ± 0.3 | 1.0* |
| | 800 | 6 | 2.8 ± 1.1 | 1.5 ± 0.4** | 2.1 ± 0.3*** |
| | 1,200 | 3 | 2.2 ± 0.8 | 1.8 ± 0.3 | 1.7 ± 0.3 |
| C _{max} (μg/mL) | 200 | 3 | 10.552 ± 6.042 | 6.669 ± 3.698 | 6.354 ± 3.775 |
| | 400 | 3 | 11.667 ± 3.807 | 7.212 ± 1.060 | 6.351* |
| | 800 | 6 | 14.620 ± 5.649 | 10.564 ± 1.831** | 10.732 ± 4.690*** |
| | 1,200 | 3 | 16.004 ± 1.910 | 8.148 ± 4.219 | 6.706 ± 0.884 |
| AUC _{0-t} (μg h/mL) | 200 | 3 | 45.6 ± 21.0 | 20.6 ± 6.2 | 21.2 ± 9.5 |
| | 400 | 3 | 58.2 ± 16.8 | 25.0 ± 9.4 | 22.9* |
| | 800 | 6 | 83.3 ± 32.7 | 44.6 ± 17.3** | 30.0 ± 16.7*** |
| | 1,200 | 3 | 76.6 ± 1.0 | 32.9 ± 16.2 | 25.8 ± 2.4 |
| T _{1/2} (h) | 200 | 3 | 8.03 ± 3.82 | 4.80 ± 2.14 | 3.59 ± 1.71 |
| | 400 | 3 | 7.89 ± 4.04 | 3.53 ± 0.43 | 5.36* |
| | 800 | 6 | 9.93 ± 6.01 | 4.31 ± 2.72** | 4.37 ± 4.05*** |
| | 1,200 | 3 | 8.33 ± 4.65 | 2.78 ± 0.90 | 4.84 ± 3.29 |

* 2 patients, ** 5 patients,
*** 4 patients

Fig. 2 Effect of dose on the C_{max} and AUC

TSU-68 increased to reach C_{max} at ~2.5 h and thereafter disappeared with T_{1/2} in ~8–10 h. At the any dose levels, C_{max} and AUC_{0-t} after the repeated doses on days 8 and 29 were ~2-fold lower than those after the first doses on day 1. These parameters are not statistically different between days 8 and 29. In addition, no obvious dose-dependent increase in plasma exposure to TSU-68 repeatedly administered was observed over the four dose levels, most notably the higher dose levels. Urinary excretion of TSU-68 was below 1% of dose at the any dose levels.

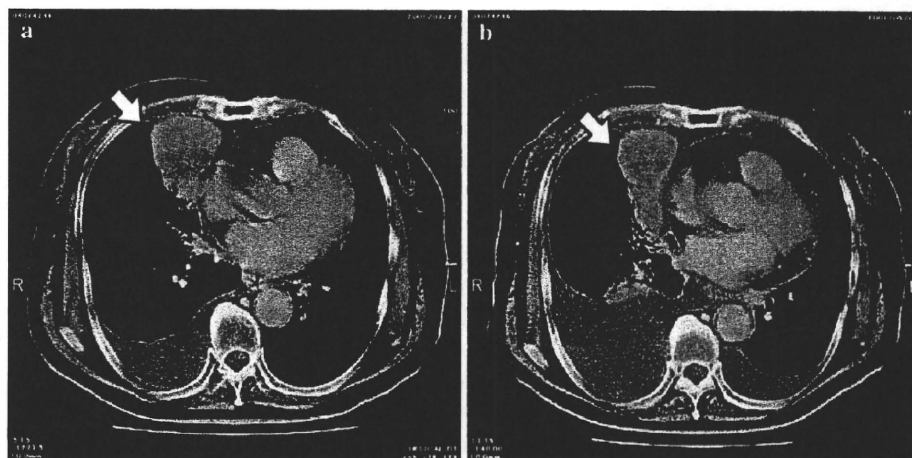
Response

No partial or complete responses were seen. One patient with adenocarcinoma of the lung had a minor response by 4 week

treatment (Fig. 3) and continued 3 months, but after that the treatment discontinued because of tumor progression and drug-related toxicity. The increased effusion was confirmed non-malignant, and this event was considered a drug-related toxicity. The size of the target lesion reduced from 5.5 cm × 5.0 cm of the base line to 4.5 cm × 4.3 cm of 4 week treatment (29.6% reduction). Reduction of tumor marker levels was seen in the same patient (CEA 22.6 → 12.6 ng/ml, SLX 74 → 58 U/ml). Four patients had stable disease (non-small cell lung cancer 2; thymoma 1; peritoneal sarcoma 1) and continued treatment over two cycles until disease progression (until 5 cycle for patients with peritoneal sarcoma and 2 cycles for the rest of the patients).

In the angiogenesis-related biomarker of the six tested factors with 14 patients, not including one patient of DLT,

Fig. 3 Computed tomography scan of a tumor minor shrinkage in a patient with adenocarcinoma of the lung, and pleural effusion progression, treated with TSU-68. **a** Baseline; **b** week 4. *White arrow* primary tumor in the lung



an average of PAI-1 and urine VEGF saw an increase of more than 20% over the baseline (from 24.3 ± 6.7 ng/ml to 29.5 ± 11.3 ng/mL and from 96.6 ± 62.4 pg/ml to 132.1 ± 93.6 pg/mL, respectively), but plasma VEGF, E-selectin, tPA and VCAM-1 were not changed substantially.

Discussion

We performed a phase I and pharmacokinetic study to explore safety, tolerated dose, and pharmacokinetics of the oral multiple tyrosine kinase inhibitor TSU-68 in Japanese patients with advanced solid tumors. In this study using continuous oral bid administration between meals, side effects attributable to the study drug were subjective/objective symptom and abnormal changes in laboratory values, whereas DLT included arrhythmia.

The subjective and objective symptom toxicities of TSU-68 in our current study were predominantly gastrointestinal and consisted of dose-dependent, non-cumulative, and reversible diarrhea, fatigue, anorexia, and abdominal pain. At lower dose levels, these symptoms were mild and needed no additional treatment. At the highest dose level, 2 patients discontinued the treatment over 4 weeks for intolerable fatigue and abdominal pain, respectively (Table 2). Some patients with abdominal pain were given gastrointestinal endoscopy, but no remarkable finding was observed. It was considered a reasonable assessment to stop the dose escalation under grade 2 fatigue and grade 2 abdominal pain at a dosage level of $1,200$ mg/m² bid, because of unacceptable adverse events for an antitumor drug that is used in long-term consecutive oral administration.

In 7 patients, edema and/or pleural effusion progression were seen as dose independent (for example: Fig. 3). Edema was remarkable on the face and eyelids. In addition, 11 patients experienced hypoalbuminemia dose dependently. Although this was seen from an early period, it

improved immediately after therapy discontinuance. Although VEGF is also known as a vascular permeability factor [20, 21], the contribution of VEGF is unclear with no significant difference between patients with edema or effusion progression and patients without. VEGF level in pleural effusion was not elevated in some patients (data not shown). On the other hand, there is a possible contribution of PDGF in this phenomenon based on the report that edema was seen in about 40% patients including 7% grade 3/4 treated with Imatinib, which is an inhibitor of Bcr/Abl tyrosine kinase and PDGF/Kit tyrosine kinase and approved for chronic myeloid leukemia, Philadelphia chromosome positive acute lymphoblastic leukemia and gastrointestinal stromal tumor [22–24]. It was also reported that PDGF levels of pleural effusion with lung cancer were higher than in non-malignant pleural effusions [25].

Six patients experienced tumor pain progression such as chest pain from primary or metastatic lung cancer. This may be due to drug intake, because tumor pain was diminished after being taken off the drug. To clarify the mechanism of these symptoms, additional studies including basic research are needed.

The hematologic toxicity of TSU-68 in the current study was considered dose independent. Grade 3 anemia and thrombocytopenia were seen in the same patient at 800 mg/m² dose level. Thrombocytopenia was recovered to pre-treatment level after treatment discontinuance, but anemia continued. This patient was given radiotherapy after 9 days due to bone metastasis. Therefore, anemia was not attributed to TSU-68 intake but tumor progression.

These toxicity findings, characterized as edema, were much different from the reports of recent approved and developing angiogenesis inhibitors showing bleeding, perforation, hypertension, hand-foot syndrome, and some leukocytopenia as the distinguishing toxicity profile [26–28].

In the pharmacokinetics, the C_{max} and AUC were similar between days 8 and 29, although decreased by half after the

repeated administration of TSU-68. This suggests that the decreased plasma exposure to TSU-68 rapidly reaches the steady state and is maintained over therapeutic cycles. This trend is consistent with a published clinical result showing that AUC of TSU-68 on day 56 was similar to that on day 28 [29]. In addition, at the higher dose levels, there was no dose-dependent increase in these parameters of TSU-68 repeatedly administered, which is probably due to a saturation of absorption. The trough plasma level in the steady-state exposure to 200 mg/m² TSU-68 is above the IC₅₀ for VEGF and PDGF receptors cellular assay, and the exposure was also comparable with that showing efficacy in human cancer xenograft models [16]. The decrease in the exposure after repeated administration is probably due to autoinduction of TSU-68 metabolism. Since urinary excretion accounted for a very low percentage of the dose, predominant elimination of TSU-68 can be regarded as hepatic metabolism. Non-clinical studies [30, 31] suggest that TSU-68 causes induction of liver cytochrome P450, CYP1A1/2 involved in its own metabolism, leading to the decrease in the TSU-68 plasma concentrations.

A phase I study of the United States was reported before our Japanese study. Nineteen Caucasian patients were treated at doses ranging from 400–1,200 mg/m² fasted and 100–400 mg/m² fed by twice daily administration [32]. Dose-limiting toxicities including fatigue, pleuritic chest pain, shortness of breath, and pericardial effusions were seen in 2 patients. The AUC declined from 70 µg.h/ml on day 1 to 32 µg.h/ml on day 28. The results for TSU-68 in Japanese patients demonstrated a similar toxicity and pharmacokinetics profile to Caucasian patients.

Antitumor effect was observed in some patients in this clinical study. One patient with adenocarcinoma of the lung had a minor tumor shrinkage and reduction of tumor marker levels. In addition, four patients had no disease progression after one cycle treatment. Although angiogenesis inhibitors such as TSU-68 have been thought to have little or no tumor shrinkage, some drugs showed obvious tumor regression.

Although the primary objective of phase I clinical trial is not to see response but to determine recommended dose for phase II clinical trial, tumor response is thought to be an important factor. Therefore, further studies using this agent are expected. MTD was not reached in this study, because DLT was only seen in one patient at 800 mg/m². We suggest the highest dose level was not the tolerable dose, because two patients discontinued the treatment for drug-related toxicities in spite of their being low grade. In addition, pharmacokinetic data of this level showed no significant difference compared with other dose levels, and no dose-dependent increase on days 8 and 29.

In conclusion of this phase I and pharmacokinetic study with continuous oral bid between meals, TSU-68 has shown

that a multiple receptor tyrosine kinase inhibitor can be safely administered. The recommended dose for further studies using this treatment schedule is less than 800 mg/m² bid.

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