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CLINICAL TRIAL REPORT

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A phase IB clinical and pharmacokinetic study of the angiogenesis inhibitor SU5416 and paclitaxel in recurrent or metastatic carcinoma of the head and neck

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Abstract *Purpose*: SU5416 is a novel small organic molecule that non-competitively inhibits the phosphorylation of the VEGF tyrosine kinase receptor, Flk-1. This phase IB study was performed to determine the safety, pharmacokinetics, and preliminary efficacy of the combination of SU5416 and paclitaxel in recurrent or metastatic carcinoma of the head and neck. *Methods*: Enrolled in the study were 12 patients with biopsy-proven recurrent or metastatic carcinoma of the head and neck. Six patients received intravenous SU5416 110 mg/m^2 on days 1, 15, 18, 22 and 25, and paclitaxel 70 mg/m^2 on days 8, 15 and 22. Since two patients experienced a dose-limiting toxicity (DLT) in cohort 1, the next six patients received identical treatment as above except the paclitaxel dose was reduced to 55 mg/m^2 per week. *Results*: A total of 42 cycles at two different dose levels were given. In cohort 1 there were two deep venous thromboses that were DLTs. In the second cohort there was a DLT consisting of a transient ischemic attack after receiving SU5416. Most of the other toxicities seen were grade 1 or 2 in nature and consisted of headache, facial flushing, and fatigue. Two patients developed extensive ulcerative cavities at sites of prior radiation. There were no significant changes in the pharmacokinetic parameters of SU5416 given with paclitaxel. Four patients had prolonged freedom from progression of 18, 28, 42, and 60 weeks duration. *Conclusions*: The combination of SU5416 with paclitaxel had a higher than expected incidence of thromboembolic events and prophylactic anticoagulation should be considered for future trials that combine an angiogenesis inhibitor with cytotoxic chemotherapy. Although the future development of SU5416 as a chemotherapeutic agent is unclear, there was a clinical benefit seen with this combination in 36% of the patients. This trial supports the use of developing antiangiogenic combinations, using molecular targeted agents, in head and neck carcinoma.

Keywords SU5416 · Paclitaxel · Angiogenesis inhibitor · Head and neck cancer · VEGF tyrosine kinase receptor

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Introduction

Patients with recurrent or metastatic head and neck cancer have a poor prognosis with a median survival of

6 months and a 1-year survival of 20% [1]. A variety of chemotherapy regimens have been tried and single-agent chemotherapy with cisplatin, carboplatin, 5-fluorouracil, or paclitaxel have demonstrated response rates from 15 to 30%. [2–6]. Combination therapy trials of a platinum-based therapy with paclitaxel, bleomycin, vincristine, or 5-fluorouracil have demonstrated response rates of 31–39% with no significant improvement in survival compared to single-agent regimens [7–12].

Due to the poor prognosis of recurrent or metastatic head and neck carcinomas, new treatment approaches need to be explored. Agents that target the blood supply to the tumor (i.e., angiogenesis inhibitors) have been proposed as an approach to treating head and neck tumors. Specifically agents that inhibit proangiogenic peptides, such as vascular endothelial growth factor (VEGF), may limit the tumor's blood supply as well as decrease subsequent tumor growth and metastases.

SU5416 is a novel small organic molecule that non-competitively inhibits the phosphorylation (and hence intracellular signaling) of the VEGF tyrosine kinase receptor, Flk-1, with an IC_{50} of approximately 1 μM in Flk-1-overexpressing NIH 3T3 cells [13]. Additionally, SU5416 inhibits VEGF-induced mitogenesis of endothelial cells in a dose-dependent manner with an IC_{50} of approximately 0.04 μM without direct inhibitory effects on in vitro growth of several cell lines [13]. SU5416 has been evaluated in a phase I study with the maximum tolerated dose of 145 mg/m^2 per week; dose-limiting toxicity (DLT) consisted of projectile vomiting and headache at 190 mg/m^2 [14].

Paclitaxel's mechanism of action has traditionally been attributed to its ability to induce stabilization of the cellular microtubule apparatus and therefore interfere with cell division as well as other vital cellular processes [15]. Microtubule-stabilizing agents have been demonstrated in both in vitro and in vivo models to inhibit angiogenesis. Human umbilical venous endothelial cells, which proliferate in response to angiogenic factors bFGF and VEGF, show a decrease in vascular proliferation after exposure to a taxane [16]. This inhibition of vascular growth is increased when an antiangiogenic compound is also given [17]. In a mouse model microtubule-stabilizing agents have also been demonstrated to inhibit endothelial cell proliferation, motility, and invasiveness in a dose-dependent manner [18].

Although paclitaxel as a single agent has demonstrated only modest efficacy in patients with advanced head and neck cancer, preclinical data has demonstrated that the combination of a chemotherapy agent (i.e., paclitaxel) with an angiogenesis inhibitor (i.e., SU5416) may produce a greater tumor response than either agent alone [19]. This phase IB study was therefore performed to determine the safety, pharmacokinetics, and preliminary efficacy of the combination of SU5416 and paclitaxel in recurrent or metastatic carcinoma of the head and neck.

Patients and methods

Eligibility

Patients with histologically verified metastatic or locoregionally recurrent squamous and non-squamous cancer of the head and neck that was incurable by surgery or radiation therapy were included. Only patients older than 18 years with an ECOG performance status ≤ 2 and a life expectancy of at least 12 weeks were eligible. Adequate hematologic (WBC $>3500/\mu l$, platelets $>100{,}000/\mu l$, and hemoglobin >9.0 g/dl), renal (serum creatinine <1.5 mg/dl), hepatic (bilirubin <1.5 mg/dl, and AST and ALT less than two times normal), and prothrombin time (PT) and partial thromboplastin time (PTT) within normal limits were required for eligibility. Prior chemotherapy and/or radiation were allowed as long as at least 4 weeks had elapsed and all acute side effects resolved. Patients with a known hypercoagulable syndrome, or if they had a deep venous thrombosis (DVT), pulmonary embolism, or arterial thrombosis within 6 months prior to study were excluded. All patients gave informed consent according to institutional and FDA guidelines before entry into the study.

Study design

SU5416 (NSC 696819) was supplied by the Pharmaceutical Management Branch of CTEP, at the NCI. Six patients were enrolled in cohort 1. During cycle 1 all patients received intravenous SU5416 110 mg/m^2 on days 1, 15, 18, 22 and 25, and paclitaxel 70 mg/m^2 intravenously on days 8, 15 and 22. For cycle 2 and beyond SU5416 was given on days 1, 4, 8, 11, 15, 19, 22 and 25, with paclitaxel administered on days 1, 8, 15 and 22. One treatment cycle was 4 weeks and patients were restaged after two cycles (8 weeks). Cohort 2 was treated identically to the first cohort except the dose of paclitaxel was 55 mg/m^2 per week. The use of hematopoietic growth factors was not permitted. All patients who received SU5416 via a central line received warfarin 1 mg daily in order to minimize the risk of pulmonary embolism.

All patients were evaluated weekly to assess for any drug-induced toxicity using the NCI Common Toxicity Criteria version 2.0 (NCI, CTC, bound booklet under separate cover and web site http://ctep.info.nih.gov. A DLT was defined as any grade 3 or more non-hematologic event or grade 4 or more hematologic event. All patients who received a minimum of two cycles of treatment (8 weeks) or those patients who developed early progressive disease were considered evaluable for response using standard RECIST criteria [20].

Pharmacokinetic analysis

Patients were admitted to the General Clinical Research Center (GCRC) at University Hospitals of Cleveland for 24 h on days 1, 8 and 15 of cycle 1 for serum collection.

Table 1 Patient baseline characteristics and response data (*SCC* squamous cell cancer, *PD* progressive disease, *SD* stable disease, *NE* not evaluable)

Patient number	Tumor type	Age (years)	Gender	SU5416 mg/m^2 twice a week	Paclitaxel mg/m^2 per week	No. of cycles	Best response	Duration of SD (weeks)
1	SCC tongue	68	Male	110	70	1	PD	–
2	Medullary thyroid	63	Male	110	70	14	SD	60
3	SCC lip	68	Male	110	70	5	SD	28
4	Adenocarcinoma nasopharynx	50	Male	110	70	8	SD	42
5	SCC nasopharynx	44	Male	110	70	2	PD	–
6	SCC buccal mucosa	51	Female	110	70	1	PD	–
7	SCC tongue	55	Female	110	55	1	PD	–
8	SCC nasopharynx	46	Female	110	55	1	NE	–
9	Adenocystic submandibular gland	61	Female	110	55	2	PD	–
10	SCC retromolar trigone	67	Female	110	55	2	PD	–
11	Myoepithelial salivary gland	65	Male	110	55	1	PD	–
12	Medullary thyroid	46	Male	110	55	4	SD	18

The rest of the infusions were given in the Cancer Center outpatient facility. The plasma samples for SU5416 determination were collected before the infusion and at 30, 60, 65, 70, 75, 90, 105, 120, 180, 300 and 420 min. The paclitaxel samples were obtained before the infusion, at the end of the infusion, and at 30, 60, 90, 120, 240, 360, and 480 min. After separating plasma, the samples were kept frozen at −60°C. SU5416 in plasma was analyzed with a high-performance liquid chromatographic method developed and validated by Sugen (South San Francisco, Calif.) [21]. Paclitaxel concentrations were determined in plasma with the high performance liquid chromatographic method of Willey et al. [22] with modification.

A one-compartment open model following a 60-min infusion regimen was fitted to the SU5416 plasma concentration versus time curves using the PKanalyst program (MicroMath Scientific Software, Salt Lake City, Utah). The elimination $t_{1/2}$ was derived from the terminal slope using the equation $t_{1/2} = 0.693/\text{Kel}$. Total clearance (Clp) is calculated from the model independent approach using Clp = D/AUC, where AUC is the total area under the plasma concentration versus time curve and D is the dose [23, 24]. The volume of distribution (Vd) was calculated from the relationship of Vd = Clp/Kel.

Statistical analysis

Student's *t*-test was used for the comparison among different doses and between weeks in a treatment cycle. *P* values less than 0.05 were regarded as significantly different.

Results

Patient characteristics

Enrolled in the study were 12 patients (7 men and 5 women) with recurrent or metastatic head and neck cancer. A total of 42 cycles were given at two different dose levels. Patients were enrolled from June 2000 through July 2002. The last patient came off study in November 2002. All of the patients were Caucasian and the median age was 56 years (range 44–68 years). The patients showed a variety of head and neck squamous and non-squamous tumor histologies. Baseline characteristics and response data for the patients are listed in Table 1.

All 12 patients underwent surgery prior to study enrollment. Five of the 12 patients underwent a modified radical neck dissection. Eight patients also underwent radiotherapy prior to this study. Six patients received systemic chemotherapy, either as single agents or in combination, prior to enrolling in the study.

Toxicities

The clinical toxicity observed in cycle one is summarized in Table 2. In cohort 1 there were two episodes of DLT consisting of a right lower extremity DVT and an upper extremity DVT at the site of a central catheter. A patient

Table 2 Cycle 1 toxicity ($n = 12$). Values are the number of patients experiencing each adverse event as defined by NCI Common Toxicity Criteria version 2.0. Only those grade 1 and 2 toxicities seen in 25% or more of patients are listed. All grade 3 toxicities are listed. There were no grade 4 or 5 toxicities (*DVT* deep venous thrombosis, *PTT* partial thromboplastin time, *PT* prothrombin time, *TIA* transient ischemic attack)

Toxicity	Grade			
	1	2	3	4
DVT	0	0	2	0
Dizziness	0	0	1	0
Dysphagia	0	0	1	0
Facial flushing	4	0	0	0
Fistula	0	0	1	0
Fatigue	3	0	0	0
Headache	4	4	0	0
Lymphopenia	0	1	5	0
Motor neuropathy	0	0	1	0
Nausea	6	0	0	0
Prolonged PTT	0	0	1	0
Prolonged PT	0	0	1	0
TIA	0	0	1	0

in cohort 2 experienced an episode of aphasia, right facial droop, and right upper extremity weakness approximately 18 h after her first dose of SU5416. She had complete resolution of all symptoms 3 h after their onset. A subsequent MRI scan revealed acute ischemic changes of the left frontal and parietal areas and an MR angiogram was unremarkable. The patient was diagnosed as having a transient ischemic attack and was removed from the study. The most common grade 1 or 2 toxicities consisted of headache, facial flushing, and fatigue. There were five episodes of grade 3 lymphopenia and there were no grade 4 toxicities or treatment-related deaths.

Two of the eight patients, who received radiotherapy prior to study enrollment, developed progressive ulcerations at the site of prior radiotherapy. A 71-year-old male with recurrent squamous cell carcinoma of the tongue and right lateral jaw developed a 2.5 cm tumor ulcer at the site of prior right jaw radiotherapy after completing cycle 1. A 68-year-old male with squamous cell carcinoma of the lip with involvement of the left buccal mucosa developed a 7.5×8.0 cm ulcer on his left oral cavity at the site of prior radiation after five cycles (28 weeks) of therapy (see Fig. 1). Tumor recurrence was demonstrated from a tissue sample taken from the periphery of this ulcerative cavity.

Pharmacokinetic analysis

On day 1, all patients received SU5416 110 mg/m^2 only and the $t_{1/2}$ was 35.3 ± 4.3 min, C_{max} 2760 ± 301 ng/ml, AUC 239,911 ± 35,709 min ng/ml, Vd 23.5 ± 2.5 l/m^2, and Cl 467 ± 70 ml/min m^2. On day 15, SU5416 and paclitaxel were both given and the pharmacokinetic values of SU5416 were $t_{1/2}$ 35.6 ± 5.2 min, C_{max} 3061 ± 451 ng/ml, AUC 265,643 ± 36,058 min ng/ml, Vd 21.6 ± 4.0 l/m^2, and Cl 422 ± 65 ml/min m^2. There was no significant change of any SU5416 pharmacokinetic parameter with the addition of paclitaxel (Table 3).

On day 8, paclitaxel pharmacokinetic parameters at either 55 or 70 mg/m^2 were $\alpha_{1/2}$ 8.5 ± 0.7 min, $\beta_{1/2}$ 172 ± 28 min, $t_{1/2}$ 13.1 ± 1.6 min, C_{max} 1701 ± 505 ng/ml, AUC 144,173 ± 44,353 min ng/ml, Vd 7.8 ± 2.9 l/m^2, Vd_{ss} 41 ± 16 l/m^2, and Cl 414 ± 138 ml/min m^2. On day 15, patients received both paclitaxel and SU5416 and the paclitaxel pharmacokinetic values were $\alpha_{1/2}$ 6.4 ± 1.4 min, $\beta_{1/2}$ 175 ± 24 min, $t_{1/2}$ 12.3 ± 2.8 min, C_{max} 1738 ± 512 ng/ml, AUC 170,680 ± 43,707 min ng/ml, Vd 6.1 ± 2.1 l/m^2, Vd_{ss} 45 ± 16 l/m^2, and Cl 340 ± 88 ml/min m^2 (Table 4). These data are consistent with prior published data of paclitaxel pharmacokinetics [25–27]. The only significant parameter demonstrated was a slight increase in the AUC of paclitaxel, at the 55 mg/m^2 dose level, with the administration of SU5416.

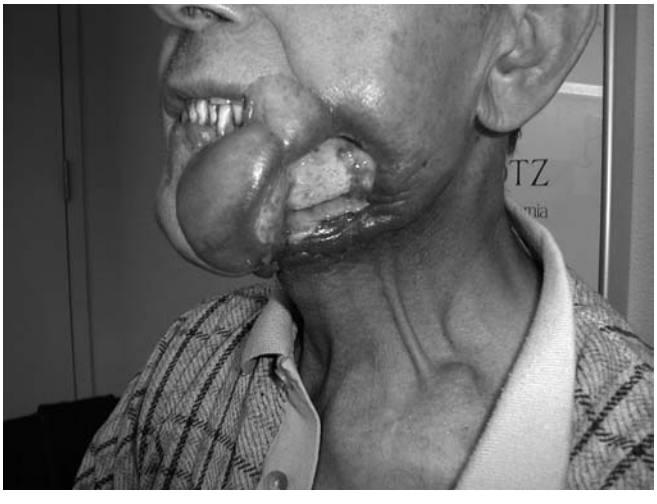

Fig. 1 Photograph of a 68-year-old male with squamous cell carcinoma of the lip initially treated with repeated surgical resections, radiotherapy and concurrent 5-fluorouracil-based chemotherapy. Prior to beginning this trial he had a 2.0×3.0-cm soft tissue mass adjacent to the mandible. After cycle 1 this area developed an ulcerative lesion that eventually increased in size to 7.5×8.0 cm after five cycles (28 weeks) of therapy. We hypothesize that the tumor may be undergoing apoptosis with compromise of the vascular supply by the SU5416 and paclitaxel and therefore created a necrotic ulcerative cavity

Response

Of the 12 patients enrolled in the study, 11 were evaluable for response. The patient who experienced a transient ischemic attack after day 1, cycle 1, of SU5416 was taken off study and was not considered evaluable for response. Four patients had prolonged periods of stable disease, three in cohort 1 and one in cohort 2. The three patients in cohort 1 comprised: a 62-year-old male with metastatic medullary thyroid cancer to bone, liver, and epidura who was treated for 14 cycles and had stable disease for 60 weeks; a 50-year-old male with nasopharyngeal adenocarcinoma with invasion into the right maxillary sinus and orbit who received a total of eight cycles with stable disease for 42 weeks; and a 68-year-old male with squamous cell carcinoma of the lip with persistent local disease who received five cycles with stable disease for 28 weeks. The patient with stable disease in cohort 2 was a 46-year-old male with medullary thyroid cancer with persistent local disease who received four cycles of therapy with freedom from progression for 18 weeks. Seven patients had progressive

Table 3 Pharmacokinetic parameters of SU5416 (110 mg/m^2, $n = 6$) alone on week 0 and with paclitaxel (55 or 70 mg/m^2) on week 3 in patients with head and neck malignancy ($t_{1/2}$ half-life, C_{max} maximal concentration, *AUC* area under the curve, *Vd* volume of distribution, *Cl* clearance, *NS* not significant)

Parameter	Week 1	Week 3	*t*-test
$t_{1/2}$ (min)	35.3 ± 4.3	35.6 ± 5.2	NS
C_{max} (ng/ml)	2,760 ± 301	3,061 ± 451	NS
AUC (min ng/ml)	239,911 ± 35,709	265,643 ± 36,058	NS
Vd (l/m^2)	23.5 ± 2.5	21.6 ± 4.0	NS
Cl (ml/min m^2)	467 ± 70	422 ± 65	NS

Table 4 Pharmacokinetic parameters of paclitaxel (55 mg/m^2, $n=6$) alone and together with SU5416 (110 mg/m^2) ($t_{1/2}$ half-life, C_{max} maximal concentration, AUC area under the curve, Vd volume of distribution, Vd_{ss} volume of distribution steady state, Cl clearance, NS not significant)

PK parameters	Paclitaxel alone	Paclitaxel with SU5146	*t*-test
$\alpha_{1/2}$ (min)	8.5 ± 0.7	6.4 ± 1.4	NS
$\beta_{1/2}$ (min)	172 ± 28	175 ± 24	NS
$t_{1/2}$ (min)	13.1 ± 1.6	12.3 ± 2.8	NS
Cmax (ng/ml)	1,701 ± 505	1,738 ± 512	NS
AUC (min ng/ml)	144,173 ± 44,353	170,680 ± 43,707	0.03
Vd (l/m^2)	7.8 ± 2.9	6.1 ± 2.1	NS
Vd_{ss} (l/m^2)	41 ± 16	45 ± 16	NS
Cl (ml/min m^2)	414 ± 138	340 ± 88	NS

disease after the first two cycles and were taken off study.

Discussion

Until 1971 it was proposed that tumors lay dormant in situ for months to years, rarely growing beyond 2–3 mm^3 in maximum size until the development of neovascularization [28]. When a tumor becomes vascularized, a subgroup of cells "switches" to an angiogenic phenotype with the emergence of markedly increased tumor growth, tumor cell invasion, and ultimately dissemination [29].

The VEGF tyrosine kinase receptors (Flt-1 and Flk-1/KDR) are expressed on endothelial cells and have been implicated in the angiogenesis associated with a variety of human carcinomas including oral cavity tumors [30–32]. SU5416 is a potent and selective inhibitor of the VEGF receptor (Flk-1/KDR) that has been demonstrated in vivo to inhibit tyrosine kinase catalysis, tumor vascularization, and growth of a variety of tumor types [13]. Single-agent SU5416 has been evaluated in a phase I study of solid tumors. The maximal tolerated dose is 145 mg/m^2 per week, with the most serious toxicities being headache associated with nausea and projectile vomiting [14].

Subsequent trials have evaluated both single-agent SU5416 and SU5416 in combination with other chemotherapies in a variety of tumor types. The incidence of thromboembolic events associated with single-agent SU5416 has been reported as 2.2% [33]. However, in a phase I dose-escalation trial in solid tumors SU5416 was combined with cisplatin and gemcitabine and among 19 treated patients, 8 (42%) developed nine arterial or venous thromboembolic events (three transient ischemic attacks, two cerebrovascular accidents, and four DVT) [34]. In this study of SU5416 and paclitaxel, 3 of the 12 patients (25%) had thromboembolic events in the first cycle of treatment. Two patients developed a DVT and one patient experienced a transient ischemic attack.

The etiology of the increased thromboembolic events associated with SU5416 combined with chemotherapy is unclear. Kuenen et al. have demonstrated that by combining SU5416 with cytotoxic chemotherapy there is activation of both the coagulation cascade and endothelial cells, while chemotherapy activates only the coagulation cascade and SU5416 alone activates only the endothelial cells [35]. VEGF may play a role in both the procoagulant and the anticoagulant effect in the coagulation cascade via influencing the expression of tissue factor and thrombomodulin, increasing the vWF and factor VIII release from endothelial cells, and modulating the levels of tissue-plasminogen activator inhibitor, urokinase-type plasminogen activator, and plasminogen activator inhibitor [36–43]. The combination of SU5416 with chemotherapy may produce a net effect of shifting the coagulation cascade towards a prothrombotic state [34].

Two patients developed large ulcerative cavities at the sites of prior radiation. The mechanism of these ulcers is unclear, but we hypothesize that the tumor may be undergoing apoptosis with compromise of the vascular supply by SU5416 and paclitaxel. This could create tissue necrosis at a site already compromised by malignancy and prior radiotherapy leading to a necrotic ulcerative cavity that expands with treatment.

There was evidence of clinical benefit in 4 out of the 11 patients evaluable for response. Single-agent SU5416 and SU5416 given with paclitaxel demonstrated similar pharmacokinetic profiles. This combination had a higher than expected incidence of thromboembolic events and prophylactic anticoagulation should be considered for future trials that combine an angiogenesis inhibitor with cytotoxic chemotherapy. Although the future development of SU5416 as a chemotherapeutic agent is uncertain, there was a clinical benefit seen with this combination in 36% of the patients. This trial supports the use of developing antiangiogenic combinations, using molecular targeted agents, in head and neck carcinomas.

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