A Phase I Study of Escalating Doses of the Tyrosine Kinase Inhibitor Semaxanib (SU5416) in Combination with Irinotecan in Patients with Advanced Colorectal Carcinoma

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Background: One of the most studied pro-angiogenic factors involved in the development of colorectal cancer is the vascular endothelial growth factor (VEGF). The small molecule tyrosine kinase inhibitor semaxanib (SU5416) is one of the several agents targeting the VEGF signaling pathway, and its development centered mostly in the treatment of colorectal cancer.

Methods: We designed and conducted an NCI-sponsored trial to determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs) of semaxanib given twice weekly in combination with weekly irinotecan in patients with advanced colorectal cancer who had failed at least one prior treatment. The irinotecan dose was fixed at 125 mg/m² given weekly for 4 weeks followed by 2 weeks of rest. Patients with prior pelvic irradiation received a reduced dose of 100 mg/m². The semaxanib dose was escalated, going from 85 to 110 mg/m² and finally to 145 mg/m².

Results: Ten patients were treated in our study and all were evaluable for toxicity. There were no drug-related Grade 4 toxicities. There was one episode of Grade 3 headache and one episode of Grade 3 vomiting. The most common Grades 1 and 2 toxicities included diarrhea, abdominal cramping, anemia and nausea. Nine patients completed at least one 6 week cycle of treatment and were considered evaluable for response. Among those nine, two had a partial response, three had stable disease and four had progressive disease after the first cycle.

Conclusions: Both irinotecan and semaxanib could be given at their full single-agent recommended doses without significant toxicity, and the combination showed signs of clinical activity. However, owing to discouraging results from Phase III trials, it is unlikely that this combination will be further explored.

Key words: semaxanib – irinotecan – colon cancer – phase II – angiogenesis

INTRODUCTION

In 2004, colorectal cancer remains the third most common cause of cancer-related death in men and women in the United States (1). Although the advent of newer agents such as irinotecan (2) and oxaliplatin (3) have had a significant impact on median survival for patients with advanced disease, the majority of patients with metastatic disease remain incurable and only a fraction will be alive 5 years from the initial diagnosis. Two randomized European studies have clearly demonstrated that irinotecan is beneficial in patients with 5-FU-refractory colorectal cancer, with a median time-to-progression around 4 months (4,5). Although irinotecan has been increasingly used as a first-line treatment for metastatic colorectal cancer, the results of the intergroup N9741 study (3) have generated considerable interest in the use of oxaliplatin-based regimens in first-line treatment, increasing the interest in irinotecan as a second-line option.

The knowledge that tumors depend on new vessel formation for growth beyond a few millimeters has led to a new field of anticancer drug investigation (6). Angiogenic inhibitors reduce the ability of the tumor to develop new blood vessels, slowing or stopping its growth, not necessarily by targeting tumor cells themselves but rather by interacting with tumor-related endothelial cells. The vascular endothelial growth factor (VEGF) is one of the most important angiogenic factors in patients with colorectal cancer, and its circulating level is associated with the aggressiveness, stage and prognosis of this type of cancer (7). Therefore, the development of drugs...
targeting either VEGF or its cell surface receptor has attracted major interest. One of the earliest compounds developed was semaxanib, also known as SU5416.

Semaxanib is a potent and selective synthetic inhibitor of the Flk-1/KDR VEGF receptor tyrosine kinase. It has generated great interest due to its ability to target the VEGF pathway, and well designed in vivo and in vitro studies have helped to demonstrate its antiangiogenic potential (8–11). Semaxanib was shown to inhibit VEGF-dependent mitogenesis of human endothelial cells but to have no effect on the growth of a variety of tumor cells in vitro, confirming the VEGF receptor (VEGFR) on endothelial cells as its main target. Its systemic administration at non-toxic doses resulted in inhibition of subcutaneous tumor growth in mice, and the antitumor effect of semaxanib was accompanied by the appearance of pale white tumors in the drug-treated animals, supporting the antiangiogenic property of this agent (8).

It is believed that the effectiveness of antiangiogenic agents may be maximized when they are combined with more conventional cytotoxic agents (12,13). The different mechanisms of action and generally non-overlapping toxicity profiles make this type of combination very attractive. Theoretically, it was thought that the cytotoxic agent would reduce the number of cells while the antiangiogenic agent would reduce the formation of new vessels, starving the remaining cells. This dual effect would be expected to result in inhibition of regrowth locally and at distant sites and, hopefully, would stimulate apoptosis of the remnant cells. More recently, an alternate hypothesis has been based on the knowledge that antiangiogenic agents cause a reduction in elevated intratumoral pressure, allowing for a greater distribution of chemotherapy into tumor tissue (14).

Because of the short median time-to-progression when irinotecan is used as a second-line treatment for patients who have failed a fluoropyrimidine (5), we hypothesized that the administration of semaxanib in combination with irinotecan would be an excellent system in which to study the contribution of an antiangiogenic agent to an established cytotoxic drug. A significant increase in time-to-progression in this patient population would be clinically important and would represent an important step in the integration of antiangiogenic therapy with cytotoxic chemotherapy.

PATIENTS AND METHODS
This Phase I trial was conducted entirely at the University of Texas M. D. Anderson Cancer Center and included patients with histologically-proven, metastatic colorectal cancer whose disease had progressed after at least one, but no more than two, fluoropyrimidine-based chemotherapy regimens. Progression while on or within 6 months of adjuvant therapy was considered to qualify patients as failing a regimen for metastatic disease. Other eligibility criteria included are as follows: age above 18 years; ECOG performance status of 0–2; adequate organ function as evidenced by ANC of 1500/μl or better; platelet count of at least 100,000/μl; serum creatinine ≤1.5 mg/dl or a calculated creatinine clearance of at least 60 ml/min; and SGOT less than three times the institutional upper limit of normal. Patients had to be fully recovered from any previous treatment, and a 4 week wait period was required after surgery or radiotherapy. Both measurable and evaluable disease were acceptable; measurable disease was defined as one bidimensionally measurable lesion of at least 10 mm outside the field of any prior radiation therapy.

Patients previously treated with semaxanib, irinotecan or other topoisomerase I inhibitors were excluded from the study as were pregnant or breast-feeding women. Other exclusion criteria included are as follows: uncompensated coronary artery disease; uncontrolled diabetes; severe peripheral vascular disease; deep venous thrombosis within 3 months of entry; uncontrolled infection; serious psychiatric disorder; allergy to Cremophor® or Cremophor®-based drug products; active or uncontrolled infection; central nervous system or leptomeningeal metastasis; and history of seizure disorder or known Gilbert’s disease.

The design of this Phase I trial combined semaxanib administered twice weekly for 6 weeks with irinotecan administered weekly for 4 weeks; each cycle lasted 6 weeks. All patients received treatment through a central venous catheter, and all received 1 mg of coumadin daily as prophylaxis against thromboembolic events. On the days both drugs were administered, irinotecan was given as a 90 min infusion followed by semaxanib. The first infusion of semaxanib was administered slowly (100 cm³/h) for the first 15 min before it was increased to full speed (200 cm³/h) in order to lessen the likelihood of severe hypersensitivity reactions. If the patient was not able to tolerate the infusion rate at 200 cm³/h, it was slowed to 100 cm³/h. Owing to the Cremophor® used as a diluent for semaxanib, all patients were premedicated with antihistamines and dexamethasone. The first three doses of semaxanib were administered with a dexamethasone dose of 10 mg with a reduction to 4 mg for subsequent doses. Atropine was allowed as a treatment for cholinergic symptoms.

A total of three semaxanib dose levels were explored (Table 1) with at least three patients enrolled in each one. The irinotecan dose was fixed at 125 mg/m² given weekly for 4 weeks, followed by 2 weeks of rest. Patients who had been previously irradiated to the pelvis were treated with a reduced dose of 100 mg/m². The dose of semaxanib was escalated using three dose levels, starting with 85 mg/m² and increasing first to 110 mg/m² and finally to 145 mg/m², the dose recommended for single-agent use of this agent. The first patient at each dose level was observed for the entire first cycle before additional patients were enrolled. Additionally, the first three patients in each group completed one full cycle of treatment before we proceeded with dose escalation. Toxicities were graded using the NCI CTC (version 2). Dose-limiting toxicities (DLTs) were defined in the first cycle as Grade 3 or greater nausea and vomiting uncontrolled by aggressive antiemetic support, Grade 3 or greater diarrhea uncontrolled by aggressive antidiarrheal support, Grade 4 neutropenia or neutropenic fever, Grade 4 thrombocytopenia and any other...
non-hematological Grade 3 or greater toxicity. Subsequent cycles were not started until the treatment-related toxicities had recovered to grade \(<1\) or baseline, and if a cycle was delayed for more than 2 weeks, the patient was removed from study.

Response to treatment was evaluated after every cycle. A complete response was defined as the complete disappearance of all measurable and evaluable disease for at least 4 weeks with no evidence of new lesions. A partial response was defined as a decrease of at least 50\% in the sum of the product of all measurable disease for at least 4 weeks with no evidence of new lesions and no progression of evaluable disease. Progressive disease was defined as an increase of 25\% or greater in the sum of all measurable lesions or the appearance of any new lesions or reappearance of lesions that had disappeared. Stable disease was defined as a response that did not fit into any of the previous three categories.

Our institutional review board approved the study, and all patients provided written informed consent before enrollment and participation.

RESULTS

A total of 10 patients were enrolled and treated between April 2000 and January 2002. Their baseline characteristics are summarized in Table 2. Three patients were enrolled in each level with one additional patient enrolled at the lower irinotecan dose designed for patients who had previously received pelvic irradiation. Twenty-one cycles were delivered, with a median of two cycles (range: 1–6 cycles) per patient. Treatment was well tolerated, and the full toxicity profile is presented in Table 3. There were no drug-related Grade 4 toxicities at any of the dose levels examined. Grade 3 toxicities were restricted to two events. One patient had a Grade 3 headache that improved spontaneously without any neurological sequelae. This toxic effect is well known with the use of semaxanib and has been described in other trials with this medication. One patient had Grade 3 nausea and vomiting which improved with a more intense antiemetic regimen. Those were not unexpected toxicities, and were not considered DLTs. The most common Grades 1 and 2 toxicities included diarrhea, abdominal cramping, anemia and nausea. Some patients noted a change in urine color; a dark yellow to orange color was frequently described by patients treated with semaxanib. There were no bowel perforations and no hypertensive crisis detected among the treated patients.

Table 1. Dose levels

<table>
<thead>
<tr>
<th>Dose level</th>
<th>SU5416 mg/m²</th>
<th>CPT-11 mg/m²</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>85</td>
<td>125*</td>
<td>3</td>
</tr>
<tr>
<td>1</td>
<td>110</td>
<td>125*</td>
<td>3 (1)</td>
</tr>
<tr>
<td>2</td>
<td>145</td>
<td>125*</td>
<td>3</td>
</tr>
</tbody>
</table>

*Patients who have received prior pelvic/abdominal irradiation received irinotecan at 100 mg/m².

Nine of the ten patients included in the trial were evaluable for response. The tenth patient received treatment for five of the planned 6 weeks of the first cycle but subsequently withdrew her consent. She agreed to restaging at that time and her disease was stable, but she was considered ineligible for this efficacy analysis. Two patients (20\%) had an unconfirmed partial response, but unfortunately neither had a confirmatory scan 4 weeks later. The first patient declined further treatment and evaluation for personal reasons, and the second patient was rendered operable and was therefore removed from the study to proceed to metastectomy. Three
patients (30%) had stable disease lasting from 1 to 6 cycles, and four patients had progressive disease after the first cycle.

At this time, all patients have been removed from the study (five due to disease progression, three due to refusal to continue on study, one due to surgical resection of the disease and one due to a physician’s recommendation). The three patients who refused to continue on study voluntarily gave the following reasons for their refusal: the time required away from home, the need for a central venous catheter, and toxicity concerns.

**DISCUSSION**

The link between VEGF, angiogenesis and colorectal cancer is well established (7,9). The potential value of antiangiogenic therapy in solid tumors was demonstrated by the results of a recently published trial in which patients with previously untreated metastatic colorectal cancer were treated with either irinotecan combined with 5-FU and leucovorin (IFL) or the same regimen plus bevacizumab, a monoclonal antibody directed against VEGF (12,15). In this trial, the addition of the antiangiogenic agent resulted in a significant improvement in the response rate (from 35 to 45%) and in both the progression-free survival and overall survival, which went from 15 to 20 months.

Semaxanib is a small molecule that targets angiogenesis in a mechanistically distinct way. It binds and inhibits the tyrosine kinase activity of the VEGFR. Among the three VEGFRs, the VEGFR2 is believed to be particularly important in the pathogenesis of colorectal cancer, and therefore represents a prime target for drug development. Preclinical and clinical studies with semaxanib demonstrated that it has high affinity for the VEGFR2 receptor, and that there is indeed antiangiogenic activity associated with it. It was the first receptor tyrosine kinase inhibitor directed against VEGFR to enter clinical trials and the initial results were encouraging, leading to examining semaxanib in the first-line treatment of colorectal cancer (16). Our Phase I trial demonstrated that semaxanib at full dose can be safely combined with irinotecan in patients receiving second-line treatment for colorectal cancer. The toxicity was acceptable, and the few documented Grade 3 events were expected and easily reversible. Although the small sample size and the lack of confirmatory scans among the responding patients does not allow us to draw any conclusions on the efficacy of this regimen, responses were seen and at least one patient had an attempt at surgical resection, suggesting that this regimen was interesting enough to justify a Phase II trial as originally planned.

Even though the original plan was to proceed immediately to a Phase II trial in the same patient population, this plan was abandoned after the results from a randomized trial evaluating the addition of semaxanib to the IFL regimen showed that this agent did not improve on the results from chemotherapy alone. Additionally, semaxanib cannot be given orally. Cremophor® is used as a diluent, and a central venous catheter is needed for delivery. Further, the initial PK studies indicated that twice-a-week dosing would be required, resulting in a cumbersome regimen. The poor results in first-line treatment of colorectal cancer, associated with the introduction of next generation antiangiogenic agents with greater convenience, led to discontinuation of the active development of semaxanib for treatment of human cancer. The wisdom of the decision will only be able to be assessed over time.

**References**