Phase II Study of SU5416, a Small Molecule Vascular Endothelial Growth Factor Tyrosine Kinase Receptor Inhibitor, in Patients with Refractory Multiple Myeloma

Maurizio Zangari,¹ Elias Anaissie,¹ Alison Stopeck,² Alyssa Morimoto,³ Nguyen Tan,³ Jeffrey Lancet,⁴ Maureen Cooper,⁵ Alison Hannah,³ Guillermo Garcia-Manero,⁶ Stephan Faderl,⁶ Hagop Kantarjian,⁶ Julie Cherrington,³ Maher Albitar,⁶ and Francis J. Giles⁶

¹University of Arkansas for Medical Sciences, The Multiple Myeloma Institute for Research and Therapy, Little Rock, Arkansas; ²Arizona Cancer Center, Tucson, Arizona; ³SUGEN Inc., South San Francisco, California; ⁴University of Rochester Medical Center, Rochester, New York; ⁵Indianapolis Community Cancer Center, Indianapolis, Indiana; ⁶Department of Leukemia, The University of Texas, M.D. Anderson Cancer Center, Houston, Texas

ABSTRACT

Purpose: Increased bone marrow angiogenesis and vascular endothelial growth factor (VEGF) levels are of adverse prognostic significance in patients with multiple myeloma (MM). VEGF, a soluble circulating angiogenic molecule, acts via receptor tyrosine kinases, including VEGF receptor 2. SU5416 is a small molecule VEGF receptor 2 inhibitor.

Experimental Design: Adult patients with advanced MM were entered on a multicenter phase II study.

Results: Twenty-seven patients (median age 69, range 39–79), median 4 (0–10) lines of prior therapy, 14 with prior MM were entered on a multicenter phase II study. SU5416 at 145 mg/m² twice weekly i.v. for a median of two 4-week cycles (range 0.2–9). Grade 3/4 toxicities were rarely observed; the most frequent was thrombocytopenia (12%). Mild-to-moderate toxicities included nausea (63%), headache (56%), diarrhea, vomiting (both 37%), and fatigue (33%). There were three thromboembolic episodes and five cases of new onset hypertension. Two (7%) patients did not complete the first 4-week cycle of therapy because of adverse events (pneumonia and headache). There were no objective responses. Four patients had disease stabilization for ≥4 months. A decrease in median VEGF plasma levels was observed in patients with progressive disease (n = 7) compared with patients with progressive disease (n = 5). Overall median survival was 42 weeks (range 3–92+).

Conclusions: Although SU5416 had minimal clinical activity, signs of biological activity (decrease in plasma VEGF levels) suggest that angiogenic modulation may be of value in patients with MM.

INTRODUCTION

Increased bone marrow vascularity (angiogenesis) is part of the pathophysiology of multiple myeloma (MM; Refs. 1–4). Patients with MM have a marked increase in bone marrow microvessel density, defined as the average number of microvessels seen in a microscopic field (4–8). Increased bone marrow angiogenesis is an independent marker for adverse prognosis in patients with MM (2, 4, 6, 7, 9, 10). The degree of neoangiogenesis of the marrow consistently emerges as an independent adverse factor in models that incorporate known major prognostic factors including β₂ microglobulin, C-reactive protein, and age (4, 10, 11). The degree of abnormally elevated bone marrow angiogenesis progressively increases because patients present along the spectrum of plasma cell disorders, from the more benign monoclonal gammopathy of uncertain significance stage to advanced MM (8).

Vascular endothelial growth factor (VEGF) is the central proangiogenic molecule involved in tumor-related neovascularization (12). VEGF regulates the critical endothelial cell functions, including mitogenesis, permeability, vascular tone, and production of vasoactive molecules, involved in vessel budding and tube formation. It is also a survival factor required for the maintenance of new blood vessels (13). VEGF acts by binding to the following three receptor tyrosine kinases: vascular endothelial growth factor receptor (VEGFR)-1 (fms-like tyrosine kinase receptor-1); VEGFR-2 (kinase insert domain-containing receptor/fetal liver kinase-1); and VEGFR-3 (fms-like tyrosine kinase receptor-4; Ref. 14). Endothelial cell proliferative and mitogenic responses to VEGF, as well as changes in vascular permeability, are mediated by VEGFR-2 (15). Bone marrow vasculature and circulating VEGF levels are significantly elevated in patients with MM or plasmacytomas (4, 16–18). Decreases in median serum VEGF levels from pretherapy levels to normal levels at the time of response to first-line therapy in patients with MM have been reported (17).

As has been demonstrated in vitro with VEGF-receptor-positive blasts from patients with acute myeloid leukemia, VEGF may have a direct role in the pathophysiology of MM that is independent of its angiogenic activities (19, 20). VEGF protein is detectable in malignant plasma cells from the great majority of patients with MM (21). MM cells express VEGFR-1 (22). VEGF has been shown in vitro to directly stimulate both MM and plasma cell leukemia cell proliferation via a protein kinase C-independent Raf-1-mitogen-activated protein kinase/
extracellular signal-regulated kinase kinase-extracellular signal-regulated protein kinase pathway, and malignant cell migration via a protein kinase C-dependent pathway (22, 23). VEGF may also act as part of a paracrine loop to stimulate MM cell growth (24). Exposure of human vascular endothelial cells to VEGF increases the expression of MM-stimulatory growth factors including interleukin-6, tumor necrosis factor α, and interleukin-1β (21, 24). In addition, expression of the VEGFR-1 and VEGFR-2 is markedly elevated in the normal bone marrow myeloid and monocytic cells surrounding malignant plasma cells (21).

Z-3-[(2,4-Dimethylpyrrol-5-yl) methylidenyl]-2-indolinone (SU5416) is a small, lipophilic, highly protein-bound synthetic receptor tyrosine kinase inhibitor (RTKI) of VEGFR-2 (Fig. 1; Refs. 25 and 26). SU5416 inhibits the autophosphorylation induced by VEGF binding to VEGFR-2 by blocking the conserved AMP-binding site within the kinase domain of the receptor. SU5416 inhibits VEGF-mediated effects on endothelial cell proliferation and metabolism, both in vitro and in animal models (27, 28). SU5416 has no direct cytotoxic properties but causes dose-dependent growth inhibition in numerous xenograft tumor models, including malignant glioma, glioma, fibrosarcoma and carcinomas of the lung, breast, prostate, and skin (27). In a human colon cancer xenograft model, SU5416 inhibits metastatic spread, tumor-associated microvessel formation, and tumor proliferation (29). Phase I and II clinical studies of SU5416 in patients with solid tumors, using a twice-weekly dosing regimen, defined the maximum tolerated dose as 145 mg/m² (30). Dose-limiting toxicity at a dose of 190 mg/m² was headache, nausea, and projectile vomiting. Headaches were of 24 to 48 h duration after drug administration; refractory to standard analgesic, antiemetic, and antimigraine therapies; and fully resolved with no sequelae within 72 h. Myelosuppression or lymphopenia were not observed in phase I/II studies of SU5416 (31).

Stimulated by increasing scientific evidence for a critical role of angiogenesis in the pathophysiology of MM, therapeutic efforts focused on modulating angiogenesis are increasing (32–34). The initial agent investigated in this context was thalidomide, which has both antiangiogenic and immunomodulatory properties (35, 36). In all studies reported to date, varying rates and degrees of response to thalidomide have been documented, including in patients who have failed aggressive standard combination cytotoxic and corticosteroid therapy (37–40). Although thalidomide has consistent activity in patients with MM, there is no apparent relationship between response and suppression of excess bone marrow microvessel density and/or circulating angiogenic molecules (41). Thalidomide may not act via a specific angiogenesis-mediated mechanism in patients with MM; a specific VEGF inhibitor might therefore be more effective. On the basis of these data, a multicenter phase II study to evaluate the safety and efficacy of SU5416 in patients with refractory MM was conducted.

**PATIENTS, MATERIALS, AND METHODS**

This was an open label multicenter study to assess the efficacy and toxicity of a twice-weekly infusion of SU5416 in patients with MM. All patients gave witnessed written consent for study participation, and the Institutional Review Boards at all participating institutions approved this protocol.

**Patients.** Patients eligible for enrollment on study were 18 years of age or older with MM of one of the following types: (a) primary resistant, progressive disease during receipt of at least two courses of induction chemotherapy that includes an alkylating agent and/or a topoisomerase II inhibitor or alternate standard combination cytotoxic chemotherapeutic; (b) transiently responsive, achieved a response but relapsed while still on induction therapy; and (c) relapsed disease, achieved a response, stopped induction therapy, and then relapsed (i.e., postremission or postplateau relapse). Patients must have recovered from the toxic effects of prior therapy with a minimum interval of 7 days from prior therapy. All potentially fertile patients had to agree to use effective contraception. All at-risk female patients had to have a negative serum pregnancy test within 7 days before enrollment and every 4 weeks while on study. Patients were required to have a baseline serum bilirubin <1.5× the upper limit of normal, and serum creatinine <2.0 mg/dl patients were ineligible if they had evident active uncontrolled infection or coagulopathy, overt central nervous system disease, prior central nervous system hemorrhage, a known allergy to Cremophor or Cremophor-based drug products, an Eastern Cooperative Oncology Group performance status >2, uncontrolled cardiac disease, history of myocardial infarction, severe/unstable anemia, or uncontrolled atrial fibrillation in the 6 months before entry in the study. Patients with a known cardiac left ventricular ejection fraction of <40% were not eligible. Patients with diabetes mellitus or other disorders associated with clinical evidence of severe peripheral vascular disease or patients who had a deep venous or arterial thrombosis (including pulmonary embolism) within the prior 3 months were ineligible.

**Treatment Regimen.** SU5416 was supplied as a yellow-orange liquid formulation in vials containing 180 mg of SU5416 in 40 ml of vehicle for a final concentration of 4.5 mg/ml. Additional components of the formulation included the following: polyethylene glycol 400; polyoxy 35 castor oil (Cremophor); benzyl alcohol; and dehydrated alcohol. SU5416 was diluted with water for injection, 0.45% sodium chloride, or 0.9% sodium chloride before administration. Doses of SU5416 were administered via infusion pump at a rate of 200 ml/h except for the initial infusion, which was given at 100 ml/h for the first 15
min in an attempt to decrease the incidence of immediate-onset hypersensitivity to Cremophor (42, 43).

SU5416 was administered twice weekly through a central venous catheter between days 1 and 28 for a total of eight infusions in each 4-week cycle. Patients were to be treated until response, severe adverse event, progressive disease, or patient desire to end protocol therapy. Patients received SU5416 at a dose of 145 mg/m². Patients received premedication followed by SU5416 infusion (after at least a 30-min delay for i.v. premedication). Premedication included oral or i.v. antihistamines (25 mg of diphenhydramine or equivalent; 20 mg of famotidine or equivalent). Patients also received dexamethasone at an initial i.v. dose of 10 mg (at least 30 min before infusion) for the first three infusions. This dose was subsequently reduced to 4 mg and again to 2 mg on subsequent occasions, if tolerated. For grade 4 hypersensitivity reactions, the patient was withdrawn from the study. In the event of a grade 1 to 3 hypersensitivity reaction, the infusion was stopped and appropriate care given. Patients could receive prophylactic anticoagulation at the treating physician’s discretion as per institutional guidelines.

The primary pathway for metabolism of SU5416 is through sequential oxidation reactions of the 5-methyl group on the pyrrole ring (Fig. 1; Ref. 44). SU5416 is metabolized via the cytochrome P-450 liver enzyme, CYP1A2 (an inducible enzyme), and to a lesser extent, by CYP3A4, CYP2C9, and CYP2C19. Patients receiving drugs and agents that inhibit or induce this enzyme, including some antifungal agents (45) and macrolide antibiotics (46), may have altered plasma levels of SU5416. Recent data suggest that beverages such as coffee and grapefruit juice also inhibit CYP3A (47). These drugs or beverages were avoided while patients remained on study. Patients received full supportive care including transfusion of blood and blood products, antibiotics, antiemetics, antidiarrheals, and analgesics as appropriate. Colony stimulating factors were avoided while patients remained on study. Patients received full supportive care including transfusion of blood and blood products, antibiotics, antiemetics, anti-diarrheals, and analgesics as appropriate. Colony stimulating factors were not given to patients on study.

**Biomarkers.** Collection of plasma for determination of VEGF levels occurred during cycle 1 on days 1 and 25 before infusion. At each sampling time point, one 10-ml sample was drawn into a lithium heparin-containing Vacutainer (Becton Dickinson) and kept on ice while processed. After collection, the tube was inverted approximately 15 times to mix blood and heparin completely and processed to isolate plasma (centrifugation at 3500 rpm at 4°C for 10 min) before freezing at −20°C.

**ELISAs.** Plasma samples were assayed for human VEGF by ELISA, using kits obtained from R&D Systems, Inc. (Minneapolis, MN). All ELISAs were performed in triplicate on plasma samples according to the manufacturer’s instructions. Results were quantitated (pg/ml) based on a standard curve for VEGF.

**Evaluation and Statistics.** Complete history and physical examination were performed within 3 days of study entry. The following laboratory parameters were obtained ≤3 days before entry: complete blood count with differential; electrolyte panel, magnesium, calcium, phosphate, blood urea nitrogen, creatinine, glucose, uric acid, amylase, total protein and albumin, hepatic transaminases, bilirubin, and alkaline phosphatase; coagulation profile (prothrombin time, activated partial thromboplastin time, fibrinogen, fibrin degradation products); urinalysis; bone marrow aspirate and biopsy with histochemical, cytogenetic and immunophenotypic analysis; chest X-ray; and, for women of childbearing potential, a pregnancy test. Baseline β₂ microglobulin; serum immuno-electrophoresis, serum protein, immunoglobulin assay, and M band quantitation by immunofixation; and 24-h urine collection (Bence Jones protein, total proteins and creatinine) were performed on all patients. Additional studies (lumbar puncture with cerebrospinal fluid cytospin, computed tomography scans, bone scans, multiple gated acquisition, or echocardiogram) were performed where clinically indicated. Bone marrow specimens were obtained at baseline, day 15 and day 29 of the first cycle of therapy, every 4 weeks thereafter, as clinically indicated, and at the time of leaving the study. Physical examination, adverse event evaluation, and hematological, biochemical, and coagulation panels were repeated at weekly intervals and as clinically indicated.

All patients who received any SU5416 were considered evaluable. Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria version 2.0. Unacceptable toxicity was defined as grade 3 or greater toxicity (excluding headache, nausea/vomiting/diarrhea, and hematological toxicity) that was possibly related to SU5416 administration or grade 4 headache, nausea/vomiting/diarrhea uncontrolled by maximal medical management.

Complete response was defined as all of the following: disappearance of serum and/or urine M protein on cellulose acetate electrophoresis on two determinations at least 4 weeks apart; normal marrow with <5% plasma cells; normal peripheral blood values; no MM-attributable signs or symptoms; normal serum calcium; serum proteins; normal levels of polyclonal immunoglobulins; and resolution of all plasmacytomas. Partial response was defined as all of the following: reduction of serum M protein levels to ≤50% of baseline levels on two determinations at least 4 weeks apart and significant reduction of urine M protein levels. If the baseline value was ≥1.0 g/24 h, the level must be reduced by ≥50%. If the baseline value was 0.5–1.0 g/24 h, the level must be reduced to <0.1 g/24 h, all baseline soft-tissue plasmacytomas must reduce by ≥50% the sum of the products of the cross-diameters of each measurable lesion and decrease in bone pain from severe/moderate to mild/none. Stable disease was defined as neither complete remission, partial remission, nor disease progression; all other responses were considered failures.

As SU5416 has a noncytotoxic mechanism of action, a response rate of 10% in a very poor prognosis group of patients was considered of sufficient interest to warrant additional investigation. A maximum total of 25 evaluable patients with MM were to be entered on study. This sample size yielded an 82% posterior credibility interval for probability of response of width approximately 0.16.

**RESULTS**

**Patients.** Twenty-seven patients were enrolled and commenced therapy between December 2000 and July 2001. Baseline patient characteristics are summarized in Table 1. The patients were typical of a refractory MM population: median time from initial diagnosis was 30 months; despite relatively good performance status (only two patients had an Eastern Cooperative Oncology Group performance score of 2), over half
had moderate to severe bone pain at study entry. All patients except one had received prior chemotherapy (median of 4). Eighteen (67%) patients had failed prior therapy with thalidomide; 17 (63%) had failed prior vincristine, doxorubicin with dexamethasone therapy; 17 (63%) had failed prior autologous stem cell transplant. The median percentage of plasma cells in the bone marrow was 24% (range 6–96). Gammapathy was primarily IgG; two patients had an IgA monoclonal gammapathy. Serum M band was observed in 20 (74%) patients.

**Therapy Received.** Two patients withdrew because of rapidly progressive disease before treatment with SU5416. For the remaining 25 patients, median time on study equaled 1.7 months (range: 0.3–10.8), slightly <2 cycles of therapy (Table 2). Twenty-three (85%) patients remained on study for at least one cycle (4 weeks) of therapy; the remaining two patients withdrew early for adverse events (pneumonia with acute respiratory distress syndrome, considered unrelated to SU5416; worsening headaches, considered secondary to SU5416).

All patients received full doses of SU5416. Most patients were able to receive therapy on a twice weekly schedule [8 (32%) patients missed a single infusion]. Six (24%) patients received >2 months of therapy; the maximum number of infusions was 66, representing approximately 9 months on therapy.

**Adverse Events.** The primary toxicities were gastrointestinal (63% of patients had grade 1 or 2 nausea, frequently with diarrhea and/or emesis), together with headache (56%) and fatigue (33%). Myelosuppression was rare; however, three (12%) patients had grade 3 or 4 thrombocytopenia and two (4%) had grade 3 or 4 neutropenia. Febrile neutropenia was not observed. Bacteremia was observed in two (4%) patients; infection of the venous catheter device or cellulitis in close proximity to the device was observed in five (20%) patients. One episode each of pulmonary embolism, phlebitis, and thrombosis of the subclavian vein was observed. In addition, one patient developed a middle cerebral artery stroke with subsequent right-sided weakness. Worsening hypertension was seen in five patients with baseline hypertension, all were grade 1 or 2, with equivalent effects on systolic and diastolic levels, and all changes reversed completely and rapidly after patients ceased study therapy.

**Responses.** No objective responses were observed. Two patients had a >50% decline in serum M protein observed on single occasions (declines from 449 to 188 mg/dl and 849 to 311 mg/dl). Other patients had declines in the percentage of plasmacytosis in the bone marrow, with >50% decline seen in 5 patients, all of whom had over 50% plasma cells in the bone marrow at study entry and all of whom had stable disease on therapy. Seven patients received 3–9 cycles of therapy and were maintained with stable disease while receiving therapy. These patients then developed progressive disease and were removed from therapy.

**Biomarker Data.** Plasma VEGF levels were measured in 12 patients on days 1 and 25 of cycle 1. In samples from five patients with progressive disease, median VEGF levels were unchanged, 108.95 pg/ml on day 1 versus 108.58 pg/ml on day 25 (Fig. 2). In contrast, in seven patients with stable disease, median VEGF levels decreased from 118.77 pg/ml on day 1 to 66.44 pg/ml on day 25 (Fig. 3). Three stable disease patients had decreases (≥50%) in plasma VEGF levels whereas one stable disease patient had increased (≥50%) levels. In contrast, two of the five progressive disease patients examined had increased (≥50%) levels of VEGF. In stable disease patients, there was no apparent correlation with decreases in VEGF levels and decline in M protein, percent plasmacytosis, or extended cycles on therapy.

**Table 1** Clinical and laboratory characteristics of study patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median (range) unless otherwise indicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>69 (39–79)</td>
</tr>
<tr>
<td>Time since initial diagnosis (months)</td>
<td>30 (8–83)</td>
</tr>
<tr>
<td>Male/female (%)</td>
<td>14/13 (52/48)</td>
</tr>
<tr>
<td>Performance status (%)</td>
<td>25 (93)</td>
</tr>
<tr>
<td>Extramedullary disease (%)</td>
<td>16 (59)</td>
</tr>
<tr>
<td>Disease status (%)</td>
<td></td>
</tr>
<tr>
<td>Primary resistance</td>
<td>6 (22)</td>
</tr>
<tr>
<td>Relapse</td>
<td>21 (78)</td>
</tr>
<tr>
<td>Bone pain at baseline (%)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>6 (22)</td>
</tr>
<tr>
<td>Mild</td>
<td>7 (26)</td>
</tr>
<tr>
<td>Moderate</td>
<td>12 (44)</td>
</tr>
<tr>
<td>Severe</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Bone marrow plasma cells (%)</td>
<td>24 (6–96)</td>
</tr>
<tr>
<td>Serum M band</td>
<td>20 (74%)</td>
</tr>
<tr>
<td>IgG</td>
<td>17</td>
</tr>
<tr>
<td>Median level (g/dl) (range)</td>
<td>2.8 (0.3–8.3)</td>
</tr>
<tr>
<td>Urine M band</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>7 (26%)</td>
</tr>
<tr>
<td>Serum calcium</td>
<td>9.1 (7.6–11.0)</td>
</tr>
<tr>
<td>Total protein (g/dl)</td>
<td>8.1 (6.1–10.9)</td>
</tr>
<tr>
<td>β2 microglobulin</td>
<td>3.7 (1.6–11.7)</td>
</tr>
<tr>
<td>Total IgG (g/dl)</td>
<td>2130 (77–7770)</td>
</tr>
<tr>
<td>Total IgM (g/dl)</td>
<td>28 (0–233)</td>
</tr>
<tr>
<td>Total IgA (g/dl)</td>
<td>9 (0–7830)</td>
</tr>
<tr>
<td>Prior thalidomide therapy (%)</td>
<td>18 (67)</td>
</tr>
<tr>
<td>Prior VAD* therapy (%)</td>
<td>17 (63)</td>
</tr>
<tr>
<td>Prior SCT (%)</td>
<td>17 (63)</td>
</tr>
<tr>
<td>No. of prior regimens (%)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1 (4)</td>
</tr>
<tr>
<td>1–3</td>
<td>10 (37)</td>
</tr>
<tr>
<td>4–6</td>
<td>8 (30)</td>
</tr>
<tr>
<td>&gt;6</td>
<td>8 (30)</td>
</tr>
</tbody>
</table>

VAD, vincristine, doxorubicin with dexamethasone; SCT, stem cell transplantation.

**Table 2** Study results

| Number of evaluable patients (%)           | 25 (93)          |
| Response: n (%)                           |                |
| Complete remission                        | 0               |
| Partial remission                         | 0               |
| SD >8 weeks                               | 7 (28%)         |
| Time on study: median (max) weeks          | 7 (75)          |
| Survival: median (max) weeks               | 42 (92%)        |
| Number of nonevaluable patients (on study <4 weeks) | 2               |
| Reason for early withdrawal: progressive disease (no therapy received) | 2              |
DISCUSSION

Different modes of VEGF inhibition, including RTKI, antisense or ribozymes that target VEGF or VEGFR mRNA, soluble recombinant VEGFR, and antibodies that directly neutralize VEGF or block its receptors, are being studied in patients with hematological malignancies (19). This is the first report on a phase II study of a specific angiogenic RTKI in patients with MM. The target was the VEGFR-2 receptor tyrosine kinase using a small molecule inhibitor, SU5416. The pivotal role of VEGF in both initiating and maintaining the viability of tumor-associated vasculature renders it attractive as a therapeutic target in MM, where increased bone marrow microvessel density and increased circulating and bone marrow levels of VEGF are adverse prognostic features (8, 11). Although VEGF binds to at least three receptor tyrosine kinases, most of its biological functions related to malignancy-associated angiogenesis are mediated via VEGFR-2 (14). MM cells, however, express VEGFR-1, which may be part of a VEGF/VEGFR autocrine loop in this disease (22). A possible role of human herpes virus 8 in the pathophysiology of MM has been proposed (48). In vitro, human herpes virus 8 can transform endothelial cells via viral and cellular gene expression, which Masood et al. (49) have recently reported to be mediated in part by induction of VEGF and VEGFR. VEGF also has a major role in HIV-associated Kaposi’s sarcoma, a malignancy in which SU5416 has marked clinical activity (50, 51).

SU5416 has no general direct cytotoxic properties. Although significant regression in established tumors has been documented in one animal model (52), in most animal models SU5416 inhibits tumor growth, with tumor regrowth after cessation of therapy (25, 30). A cytostatic agent might well be of the most clinical benefit to patients with MM as a maintenance agent in relatively indolent phases of the disease [e.g. after autologous stem cell transplantation or in patients with smoldering MM (53)].

Is VEGF the best target if we wish to modulate angiogenesis in patients with MM? Although both preclinical and clinical data indicate that it has a pivotal role, other factors involved in the angiogenic regulatory cascades are present in abnormal amounts in the circulation and/or bone marrow of these patients. These include tumor necrosis factor α, interleukin-6, basic fibroblast growth factor, and hepatocyte growth factor (16, 17, 54–57).

RTKIs in development have differing patterns of inhibition of non-VEGF angiogenesis-related receptors, including those for basic fibroblast growth factor and hepatocyte growth factor (19). These latter agents may offer a broader spectrum of RTKI than SU5146 and thus be more active in patients with MM. One such agent, PTK787, inhibits in vitro MM growth via direct effects on MM cells and effects on the bone marrow microenvironment (22). Protein tyrosine kinase 787 enhances the inhibitory effect of dexamethasone on MM cells and can overcome the protective effect of interleukin-6 against dexamethasone-induced apoptosis (22).

The role for VEGF in generating and sustaining new blood vessels appears to be greatest early in tumor development (58, 59). Tumor growth, even if initially dependent on VEGF, may become independent after reaching a critical size (60). Whether the role of VEGF changes with MM disease progression is unknown, although clearly angiogenesis increases as patients move from monoclonal gammopathy of uncertain significance to active MM (8). We took the responses to thalidomide in patients with refractory MM as encouragement for the choice of VEGF as a therapeutic target and the conduct of the current study (35). Clinical responses to arsenic trioxide and the proteosome inhibitor PS-341 are postulated to be partly mediated by these agents’ angiogenesis-modulating properties (34, 61). Thalidomide is a potent suppressor of VEGF in a number of in vitro models (62). However, thalidomide has numerous other activities including suppression of basic fibroblast growth factor and tumor necrosis factor α (35, 63), both of which are present...
in excess in the circulation and bone marrow of patients with MM (64). Responses to thalidomide in patients with MM have been reported to be associated with high baseline basic fibroblast growth factor levels but not with elevated VEGF levels (37). We were unable to detect clinical improvements in patients with MM with single-agent administration of Enbrel, a soluble tumor necrosis factor receptor (55, 65). Aside from effects on angiogenic modulators, thalidomide has an array of immuno-modulatory and anti-inflammatory properties, rendering it difficult to attribute its activity in MM solely to one mechanism (35). Efforts to develop less toxic thalidomide-related compounds are under way, and the next generation of RTKI includes a number of oral agents, including SU11248, GFki258, and PKT787 (19, 20, 66, 67).

We did not restrict entry on study to patients with very high circulating VEGF levels and/or very high bone marrow microvessel density. The median pretreatment levels of plasma VEGF in the 12 patients examined from this study were lower than those reported previously in refractory MM patients (114 pg/ml compared with 223 pg/ml; Ref. 17). Although these differences might be because of the analysis of serum versus plasma, the data might also reflect inherent differences in the potential responsiveness of the patients examined. Predictive methods to identify potential responders to angiogenic modulators are obviously required. Recent data suggest that the monitoring of urinary levels of angiogenic factors may prove helpful in predicting the patients most likely to respond to VEGF RTKI (68).

The study was performed with a regimen established on a prior phase I study as having acceptable (mainly Cremophor-related) toxicities. The choice of a regimen for studies of angiogenic modulators is challenging (69). In preclinical models, SU5416 was initially considered to have antiproliferative activity on endothelial cells [human umbilical vein endothelial cells (HUVECs)] in excess of 72 h (27). Because SU5416 treatment of HUVECs does not alter surface expression of VEGFR-2 or receptor affinity for VEGF, the durability of the in vitro activity of SU5416 was originally attributed to long-lasting inhibition of VEGF-dependent phosphorylation of VEGFR-2 and subsequent downstream signaling (25, 27, 30). Early in vivo data supported dosing with SU5416 at 3- to 4-day intervals because this intermittent dosing was sufficient to inhibit tumor growth without toxicity; in certain cell lines, dosing intervals of 7 days also produced significant tumor growth inhibition (25, 30). Thus, the clinical dosing regimen on this study was of twice weekly administration during a 4-week cycle. In this study, SU5416 produced a toxicity profile similar to that reported previously. A weekly infusion of SU5416 at a dose of 145 mg/m² has been recently established to be safe and to maintain a comparatively higher systemic exposure for a given dose of SU5416 (68). Adverse events attributable to Cremophor and the need for central venous access are major problems with an agent such as SU5416, which may require chronic administration (42, 43).

Severe thromboembolic events observed in this study included central catheter-associated thrombosis, pulmonary embolism, and middle cerebral artery infarct. The majority of patients received prophylactic anticoagulation (heparin or warfarin) while on study; there was no obvious difference in the incidence of severe thromboembolic events in those patients on anticoagulation compared with those not receiving these drug [11% (2 of 19 patients) compared with 13% (1 of 8 patients)]. Of note, the incidence of catheter-related infections was high on this study, with five patients noted to have infection on study, progressing to bacteremia in two of these.

The lack of objective responses on this study was disappointing, however the 2-fold decrease in median VEGF plasma levels in patients with stable disease compared with progressive disease suggests biological activity. A similar decrease in median VEGF serum levels has been detected in MM patients responding to chemotherapy (17). Most current data indicate that antiangiogenic therapies may be cytostatic rather than cytotoxic in human malignancies (33). The assessment of these single agents in phase I studies (in which there may not be a traditional dose-limiting toxicity) and/or in phase II studies (in which objective responses may not be seen) may make the assessment of antitumor activity difficult to quantify in small phase II trials (69). The discovery of truly predictive biological markers, and a focus on disease stages in which a cytostatic agent may be beneficial, may accelerate the investigation of more targeted anticaner therapies.

REFERENCES


50. Arasteh, K., and Hannah, A. The role of vascular endothelial growth factor (VEGF) in AIDS-related Kaposi’s sarcoma. Oncologist, 50.


Phase II Study of SU5416, a Small Molecule Vascular Endothelial Growth Factor Tyrosine Kinase Receptor Inhibitor, in Patients with Refractory Multiple Myeloma

Maurizio Zangari, Elias Anaissie, Alison Stopeck, et al.


Updated version
Access the most recent version of this article at:
http://clincancerres.aacrjournals.org/content/10/1/88

Cited articles
This article cites 69 articles, 29 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/10/1/88.full.html#ref-list-1

Citing articles
This article has been cited by 12 HighWire-hosted articles. Access the articles at:
/content/10/1/88.full.html#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.