A High Rate of Venous Thromboembolism in a Multi-Institutional Phase II Trial of Weekly Intravenous Gemcitabine with Continuous Infusion Fluorouracil and Daily Thalidomide in Patients with Metastatic Renal Cell Carcinoma

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BACKGROUND. The objective of this study was to determine the clinical response rate of the combination of weekly intravenous (IV) gemcitabine with continuous infusion fluorouracil (5-FU) and daily oral thalidomide in patients with metastatic renal cell carcinoma (RCC).

METHODS. Between June, 2000 and January, 2001, 21 patients with metastatic RCC were enrolled onto this multi-institutional Phase II study of gemcitabine at 600 mg/m^2 per day on Days 1, 8, and 15; 5-FU at 150 mg/m^2 per day by continuous IV infusion through a permanent catheter on Days 1–21; and oral thalidomide on Days 1–28 starting at a dose of 200 mg daily. After the first 2 weeks of therapy, the thalidomide dose was escalated by 100 mg per day every week to a maximum dose of 400 mg per day unless it was precluded by toxicity. Treatment cycles were repeated every 28 days.

RESULTS. A high rate of venous thromboembolism (VTE) was observed. Five patients developed deep vein thrombosis (DVT), three patients developed pulmonary embolization (PE), and one patient suffered a fatal cardiac arrest preceded by hemoptysis, for an overall VTE rate of 43%. Of the 18 assessable patients, there were no complete responses and 2 partial responses (objective response rate, 10%; 95% confidence interval, 1–30%).

CONCLUSIONS. The addition of thalidomide to gemcitabine and 5-FU did not improve the objective response rate previously observed with gemcitabine and 5-FU alone and added significant vascular toxicity. The authors recommend against further development or use of this three-drug regimen. *Cancer* 2002;95: 1629–36. © *2002 American Cancer Society.*

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In the year 2001, there will be approximately 31,000 new diagnoses and 12,000 deaths from renal cell carcinoma (RCC) in the United States.[1] At the time of diagnosis, approximately 30–50% of patients with RCC will have unresectable disease.[2] About 50% of patients who undergo surgical resection for RCC with curative intent eventually will develop recurrent, incurable disease.

Patients with metastatic or unresectable disease have a poor prognosis, with a median survival of approximately 10 months.[3] Immunotherapy with interleukin-2 (IL-2), and/or interferon α leads to

objective responses in only 10–15% of patients and complete responses with long-term survival in < 5% of patients.[4]

There is no standard treatment for patients who are unresponsive to immunotherapy.[5] The best results are with fluorouracil (5-FU), which leads to a 10% overall response rate, as assessed in pooled Phase II data.[6] Multi-institutional data, however, suggest that the response rate in a more representative patient population is only 5%.[7] 5-FU is a pyrimidine analog that depletes intracellular deoxynucleotide triphosphates through inhibition of the thymidylate synthase enzyme.[8] Gemcitabine is another pyrimidine analogue that exerts cytotoxic effects predominantly by direct interference with DNA chain elongation[9] and also by inhibition of ribonucleotide reductase with a resultant decrease in deoxyribonucleotide triphosphate pools, including deoxythymidine triphophate (dTTP).[10] In vitro data suggest that combination of gemcitabine and 5-FU can deplete intracellular dTTP pools to a greater extent than either agent alone and leads to synergistic cytotoxicity.[10] We previously reported an objective response rate of 17% in patients with metastatic RCC who were treated with weekly gemcitabine and continuous infusion 5-FU.[11] The regimen was well tolerated, with fatigue and Grade 2 myelosuppression being the most common toxicities.

Recently, it was reported that thalidomide had modest single-agent activity in patients with metastatic RCC.[12] Although the mechanism of thalidomide activity in patients with RCC and other malignancies is unclear, it has been postulated that such activity is secondary to the inhibition of tumor necrosis factor α (TNF-α), vascular endothelial growth factor (VEGF), and basic fibroblast growth factor (bFGF) mRNA processing and the resultant antiangiogenic effects.[13,14] Given the potential synergism between cytotoxic and antiangiogenic agents[15] and minimal overlapping toxicities between thalidomide, gemcitabine, and 5-FU, we hypothesized that the combination of the three agents would improve on the response rate of gemcitabine and 5-FU in patients with metastatic RCC without significantly enhancing toxicity. We now show that the combination led to an unexpectedly high rate of venous thromboembolism (VTE) without any obvious increase in the overall response rate. The potential role of therapy-induced endothelial toxicity as an explanation for the high rate of VTE was explored by examining serial von Willebrand factor (vWF) levels.

MATERIALS AND METHODS

All procedures were reviewed by and in accordance with the ethical standards of the University of Chicago Institutional Review Board, and all participants provided written, informed consent.

Patient Eligibility

Patients with histologically confirmed unresectable or metastatic RCC; with a World Health Organization (WHO) performance status of 0–2; and with measurable or nonmeasurable disease, as defined by the RECIST criteria,[16] were eligible for the trial. Due to the teratogenic effects of thalidomide, all participants were required to register with the STEPS program, which required women of child-bearing potential to have a negative serum pregnancy test within 24 hours of the first dose every week for the first 4 weeks and every 4 weeks thereafter if their menstrual cycles were regular or every 2 weeks if their menstrual cycles were irregular. All women of child-bearing potential were advised to use two methods of contraception before, during, and 4 weeks after the treatment. All male participants were required to use a latex condom for each sexual intercourse they had with a woman during the treatment and for 4 weeks after the treatment. Patients were required to have adequate organ function, which was defined by the following: white blood cells $\geq 2000/mm^3$, platelets $\geq 80{,}000/mm^3$ and no platelet transfusions within 7 days, hemoglobin > 10.0 g/dL, bilirubin < 1.5 mg/dL, an aspartate aminotransferase level < 2 times the upper limit of normal, and creatinine < 2.0 mg/dL or estimated creatinine clearance > 50 mL per minute. Patients had to be at least age 18 years with a minimum recovery period of 3 weeks after any major surgical procedure and 4 weeks after chemotherapy, radiation therapy, or other investigational therapy before entry onto this study.

Patients were excluded if they had a history of another metastatic disease within the previous 5 years; active, metastatic central nervous system (CNS) disease; or prior 5-FU (or similar agents, such as FUDR, capecitabine, etc.), gemcitabine, or thalidomide treatment for metastatic RCC. Patients with CNS metastases that had been treated adequately were eligible if they did not have evidence of progressive CNS disease 8 weeks after completion of therapy and if they did not require systemic steroids or antiseizure medications. Lactating women, patients with a history of significant coronary artery disease or myocardial infarction within the previous 6 months, or patients with preexisting peripheral neuropathy $\geq$ WHO Grade 2 also were excluded from the study. After 13 patients were enrolled, the protocol was amended to exclude patients with prior history of VTE or contraindication for warfarin use (see Results, below).

Study Design

This was a Phase II, multi-institutional study that was conducted at six hospitals within a University of Chicago consortium. The treatment regimen was administered on an outpatient basis and consisted of gemcitabine 600 mg/m^2 per day over 30 minutes on Days 1, 8, and 15; 5-FU 150 mg/m^2 per day by continuous intravenous infusion through a permanent catheter on Days 1–21; and oral thalidomide on Days 1–28 starting at a dose of 200 mg daily. After the first 2 weeks of therapy, the thalidomide dose was escalated by 100 mg per day every week to a maximum dose of 400 mg per day unless it was precluded by toxicity, as described below. Treatment cycles were repeated every 28 days. Patients were re-evaluated for disease response with physical examinations and radiologic studies every two cycles using the same radiologic examinations that were used at baseline. A physician evaluated each patient at least every 2 weeks during the first cycle; if no Grade 3 or 4 toxicity was observed, then the frequency of visits could decrease to every 4 weeks for the subsequent cycles.

Therapy was continued for at least two cycles unless the patient met withdrawal criteria or had progressive disease. The National Cancer Institute Common Toxicity Criteria (version 2.0) was used to grade the toxicity. Patients who experienced Grade 3 or 4 toxicity that was attributable to therapy had further treatment withheld until such toxicity improved to $\leq$ Grade 2 (except for thalidomide-related neurotoxicity; see below), at which time therapy could be resumed with a dose reduction. Patients who experienced Grade 3 or 4 toxicities after a 50% dose reduction of gemcitabine and 5-FU were removed from the study. Patients with Grade 3 or 4 toxicity that persisted $>$ 4 weeks also were removed from the study. Patients who developed sensory-motor neuropathy or persistent somnolence $\geq$ Grade 2 had their thalidomide dose reduced to a minimum of 100 mg per day. The protocol was amended after enrollment of 13 patients to treat patients with a prophylactic dose of warfarin (1 mg per day).[17,18]

Response Assessment

The RECIST criteria were used for response assessment.

vWF Levels

Prospectively collected serum was centrifuged and stored at −70 °C. vWF levels were assessed using a commercial enzyme-linked immunosorbent assay kit (REAADS vWF antigen test kit; Corgenix, Inc., Westminister, CO) according to the manufacturer's instructions. Results are reported as the percent of normal control serum, as defined by the manufacturer.

Statistical Considerations

The purpose of this Phase II study was to assess the overall objective response rate of gemcitabine, 5-FU, and thalidomide in a population of patients with advanced or metastatic RCC. The following assumptions were made: The response rate to single-agent 5-FU was about 8%, and the response rate to combined gemcitabine and 5-FU was 17% in a multi-institution Phase II study. Therefore, a response to the three-drug combination of $>$ 20% would be considered clinically meaningful, and a response rate of $<$ 5% would lead us to conclude that the combination is inactive. Patients were accrued using a two-stage, Phase II design[19] to test the null hypothesis that the response rate was $<$ 5 percent. Twenty-one patients were to be enrolled in the first stage, and, if $\leq$ 1 response was observed, then no further patients would be accrued. If $\geq$ 2 responses were observed, then an additional 20 patients would be enrolled, for a total of 41 patients. Only if five or more responses were observed would the regimen be considered sufficiently active to warrant further investigation. With this design, the probability of accepting the drug combination if the true response rate was 5% was 0.05, and the probability of accepting the drug combination if the true response rate was 20% was 0.72. The study also included a stopping rule, such that an observed Grade 4 toxicity rate $>$ 20% would be considered unacceptable.

RESULTS

Patient Characteristics

Twenty-one patients were treated between June, 2000 and January, 2001, with 13 of 21 patients treated at The University of Chicago and 8 patients treated at affiliated institutions. Table 1 lists the patient characteristics. The median patient age was 59 years. All patients had a Cancer and Leukemia Group B performance status of 0 or 1. Fifteen patients (70%) had multiple metastatic sites. Thirteen patients (57%) had received prior systemic therapy.

Response to Treatment

Three patients were not assessable because their therapy was discontinued during the first cycle due to excessive toxicity. However, all three patients were included in the intent-to-treat analysis in determining response rates and survival (see Table 2). There were no complete responses and two partial responses (objective response rate, 10%; 95% confidence interval [95% CI], 1–30%). Nine patients experienced disease stabilization, six patients for $\geq$ 24 weeks (24 weeks,

TABLE 1
Patient Characteristics

Characteristic	Patients (n = 21) No.	%
Age (yrs)		
Median	39	—
Range	36–77	—
Gender		
Male	17	81
Female	4	19
CALGB performance status		
1	10	48
2	11	52
No. of metastasis sites		
1	5	24
2	7	33
≥ 3	9	43
Prior treatment		
Nephrectomy	19	90
Radiation therapy	4	19
Immunotherapy	13	62
Other[a]		
Flavopiridol	1	7
TNP-470	1	4
Targretin	1	4
No prior chemo/immunotherapy	8	38
Evaluable for toxicity	21	100
Evaluable for response	18	86

CALGB: Cancer and Leukemia group B.
[a] Some patients received more than one therapy.

TABLE 2
Best Response to Therapy

Best response	Patients (n = 21) No	%
Complete response	0	0
Partial response	2	10
Stable disease[a]	9	38
Progressive disease	7	33
Not evaluable	3	14

[a] The duration of computed-tomography documented stable disease was 8 weeks in 2 patients, 16 weeks in 1 patient, and ≥ 24 weeks in 6 patients.

24 weeks, 28+ weeks, 32 weeks, 36 weeks, and 52+ weeks). Both partial responders continued to maintain or improve their response even after thalidomide was discontinued (see Toxicity, below), and both were continuing therapy at 28+ weeks and 36+ weeks, respectively.

Toxicity

Toxicities are listed in Table 3. Hematologic toxicity was mild and included single episodes of Grade 4 neutropenia without fever and Grade 4 anemia. Other Grade 3 nonhematologic toxicities included fatigue (one patient), somnolence (one patient), mucositis (one patient), hand-foot syndrome (one patient), infection (nonneutropenic viral infection requiring hospitalization), diarrhea (one patient), renal toxicity (one patient), and constipation (one patient).

TABLE 3
Toxicity

Toxicity	Patients with toxicity (n = 21) Grade 2 No.	%	Grade 3 No.	%	Grade 4/5[a] No.	%
Hematologic						
Anemia	8	38	1	5	1	5
Neutropenia	7	33	4	19	1	5
Thrombocytopenia	1	5	0	0	0	0
Nonhematologic						
Cardiovascular[b]	0	0	6	29	4	19
Fatigue	4	19	1	5	0	0
Nausea/emesis	1	5	0	0	0	0
Mucositis	1	5	1	5	0	0
Peripheral neuropathy	1	5	0	0	0	0
Somnolence	1	5	1	5	0	0
Constipation	2	10	0	0	0	
Pulmonary	0	0	1	5	0	0
Renal	1	5	1	5	0	0
Edema	1	5	0	0	0	0
Infection	0	0	1	5	0	0
Hepatic	1	5	0	0	0	0
Diarrhea	0	0	1	5	0	0
Rash	1	5	0	0	0	0
Hand-foot syndrome	0	0	1	5	0	0

[a] There was only one Grade 5 cardiovascular toxicity (see table 4).
[b] One patient experienced cardiac arrhythmia exacerbation, and nine patients experienced venous thromboembolism (VTE). Table 4 provides details regarding VTE.

Venous thromboembolism (VTE) was the most common moderate-to-severe toxicity observed, accounting for 1 (5%) Grade 5 event, 3 (14%) Grade 4 events, and 5 (24%) Grade 3 events. VTE was confirmed in all patients (except patient with sudden death; see below) with radiographic studies (Doppler ultrasound, venogram, and routine or spiral chest computed tomographic scans). All VTE-related events are listed in Table 4.

Five patients were diagnosed with deep vein thrombosis (DVT) while they were on the study (two of those five patients were on prophylactic warfarin [1 mg per day] therapy at the time they were diagnosed with DVT). Of these five patients, it was found that one patient (Patient 15) had a large, metastatic tumor thrombus involving the inferior vena cava that was extracted at the time he underwent nephrectomy. The

TABLE 4
Venous Thromboembolism

	Patients with toxicity					
	Grade 3		Grade 4		Grade 5	
Toxicity	No.	%	No.	%	No.	%
Deep vein thrombosis[a]	5	24	0	0	0	0
Pulmonary embolism[b]	0	0	3	14	0	0
Other[c]	0	0	0	0	1	5

[a] Two patients were on prophylactic warfarin therapy at the time of diagnosis.
[b] One patient was on prophylactic warfarin therapy at the time of diagnosis.
[c] One patient, on prophylactic warfarin therapy, suffered a fatal cardiac arrest, which was preceded by an episode of hemoptysis.

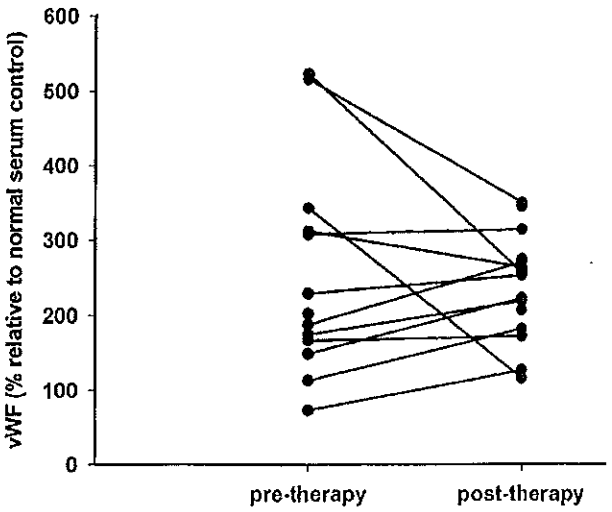

FIGURE 1. Mean baseline (pretreatment) and post-treatment von Willebrand factor (vWF) levels in available samples from 19 patients on the study. There was no consistent effect of therapy on vWF levels. No correlation was observed between baseline vWF levels or changes in vWF levels and the risk of developing venous thromboembolism.

patient complained of slowly increasing, bilateral, lower extremity swelling and was diagnosed with a large inferior vena cava thrombus during Cycle 1/Week 2 of therapy. Patient 10 was the only patient who developed catheter-associated, upper extremity DVT.

Three patients experienced pulmonary embolization (PE) while they were on the study. Patient 4 was asymptomatic, and the diagnosis of PE was established incidentally on re-evaluation imaging performed after four cycles of therapy. Patient 12 was receiving Cycle 4 of therapy when he experienced a fatal cardiac arrest at home. An autopsy was not performed, but a family member who witnessed the event reported that the cardiac arrest was preceded by an episode of hemoptysis.

In addition to the VTE events listed in Table 4, one patient (Patient 5) was hospitalized for exacerbation of atrial fibrillation during the first cycle of treatment. A retrospective review of his medical records from the hospitalization indicated that his arrhythmia exacerbation most probably was due to dehydration and anemia. However, a causal relation to the therapy could not be excluded with certainty.

Therefore, the study was suspended after enrollment of the first 21 patients demonstrated an unexpectedly high rate of VTE without any obvious improvement in the overall response rate. Five patients were on therapy when further accrual to the study was suspended, and they were advised to discontinue thalidomide but were given the option of continuing therapy with gemcitabine and 5-FU.

Serum vWF Levels

The current trial was designed prospectively to collect baseline and follow-up plasma and serum samples to measure TNF-α, VEGF, and bFGF levels to identify potential correlations with antitumor activity. Because the study was stopped early and only two partial responses were observed, these studies were not performed. Based on the known increased rate of cardiovascular events in patients who are treated with 5-FU,[20–22] we hypothesized that the combination of gemcitabine, 5-FU, and thalidomide was particularly toxic to endothelial cells, leading to the observed VTE complications. To explore this possibility, we measured vWF levels in the available pretherapy and post-therapy serum samples, because elevated vWF levels have been observed in studies of patients with various vasculitis syndromes.[23–25] The mean pretherapy and post-therapy vWF levels ($\pm$ standard deviation) in the available samples from 19 patients were 267% $\pm$ 145% and 232% $\pm$ 73%, respectively. Figure 1 shows that there was no consistent effect of therapy on vWF levels and no correlation between response and development of VTE and baseline vWF levels or changes in vWF levels (data not shown).

DISCUSSION

The paucity of good therapeutic options for patients with refractory, metastatic RCC mandates investigation of new drugs and/or drug combinations that build on existing regimens. We previously demonstrated a 17% response rate with gemcitabine and 5-FU in these patients. It had been reported that thalidomide had modest activity in patients with RCC and other disorders without significant untoward toxici-

TABLE 5
Gemcitabine and 5-Fluorouracil Based Trials

Reference	Patients enrolled	DVT / PE		Response rate	
		No.	%	No.	%
Rini et al.[11]	41	1	2.5	7	17
Ryan et al.[28]	41	1	2.5	6	14.6
George et al.[29]	21	2	10	1	10
Mani et al.[30a]	22	0	0	3	13.6
Totals	125	4	3	17	13.6

DVT: deep vein thrombosis; PE: pulmonary embolization.
[a] Only patients with renal cell carcinoma who were treated with Gemcitabine on Days 1, 8, and 15 with continuous infusion 5-fluorouracil (Days 1–21) followed by a 7-day rest were included.

ties.[12,26,27] Thus, based on potential synergism between antiangiogenic and cytotoxic agents, we hypothesized that the addition of thalidomide to the established gemcitabine and 5-FU combination would improve the response rate without a significant increase in toxicity.

The current trial was suspended after treatment of the first 21 patients, because it failed to improve on the previously reported response rates while causing a significant increase in thromboembolic toxicity. We observed 9 patients (43%) with ≥ Grade 3 thromboembolic complications that were potentially attributable to therapy. Prior to the current Phase II trial, 125 patients with RCC were treated at our institution with gemcitabine and 5-FU-based regimens that were administered in a manner similar to the current protocol.[11,28–30] Table 5 summarizes the response rates and VTE observed in those four trials. Among a similar patient population, only 4 incidents of VTE were observed among 125 patients (3%).

An important question is whether the increased risk of VTE observed in this study was due to thalidomide alone or to an interaction of thalidomide with gemcitabine and/or 5-FU. We reviewed published data from five other recent RCC trials that used thalidomide therapy without concomitant cytotoxic therapy, and a combined VTE rate of 9% (12 of 140 patients) was reported.[31–35] Data gathered regarding thalidomide-associated VTE, as reported to MedWatch, also suggest an increased risk of VTE with thalidomide therapy.[36] Within the limitations of our small study and incomplete data from other clinical trials, it seems that the incidence of VTE is higher than the incidence observed with thalidomide alone, suggesting an interaction between the three drugs. It is noteworthy that three other recently reported studies that used thalidomide in combination with cytotoxic therapy also demonstrated higher than expected VTE rates (≈ 25%), supporting such a hypothesis.[37–39]

One potential mechanism for such an interaction is that 5-FU is known to cause at least some endothelial damage (as manifested by an increased risk of coronary artery events), which then may serve as a nidus for thalidomide-mediated thrombosis. An increased serum level of vWF has been implicated previously as a potential surrogate marker for increased vascular endothelial damage. Levels of vWF are elevated at baseline in the majority of patients, as reported previously,[40,41] but there was no obvious effect of gemcitabine, 5-FU, and thalidomide combination therapy on these levels. In addition, we were unable to demonstrate a correlation between vWF levels and VTE risk, suggesting that endothelial damage is not the primary mechanism of enhanced VTE risk or that vWF levels are a poor marker of any such damage. We do note that, because of the small sample size, it is possible that vWF levels or changes in levels may have prognostic implications that we were unable to detect. Alternatively, absolute levels of vWF may not be changed by therapy, but there may be a change in the distribution of vWF multimers, as observed previously in patients with thrombotic thrombocytopenic purpura and hemolytic uremic syndrome.[42,43] The available samples collected in this study could not be used to assess this possibility. The mechanisms and the best markers for increased risk of VTE, thus, remain to be identified.

Despite addition of prophylactic warfarin (1 mg per day), we continued to observe thromboembolic complications, and further accrual to the protocol was suspended. Due to a small sample size, we are unable to draw any meaningful conclusions regarding the role of prophylactic anticoagulation, and future clinical trials with thalidomide in patients with RCC may attempt to answer such questions prospectively.

Although the results of the current study demonstrated a modest activity of the combination of gemcitabine, 5-FU, and thalidomide in patients with RCC, it was not superior to the previously reported results with combined gemcitabine and 5-FU. Because an unexpectedly high rate of VTE was observed on the trial, we recommend against further development of this three-drug combination. VTE may be a relatively under-reported toxicity associated with thalidomide, and future efforts need to be directed toward improving our knowledge of the incidence and pathophysiology of this potentially lethal adverse event.

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