Phase II Study of Lenalidomide in Patients With Metastatic Renal Cell Carcinoma

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BACKGROUND. Lenalidomide (LEN) is a structural and functional analogue of thalidomide that has demonstrated enhanced immunomodulatory properties and a more favorable toxicity profile. A Phase II, open-label study of LEN in patients with metastatic renal cell carcinoma (RCC) was conducted to determine its safety and clinical activity.

METHODS. Patients with metastatic RCC received LEN orally at a dose of 25 mg daily for the first 21 days of a 28-day cycle. The primary endpoint was the objective response rate. Time to treatment failure, safety, and survival were secondary endpoints.

RESULTS. In total, 28 patients participated in the trial and were included in the current analysis. Three of 28 patients (11%) demonstrated partial responses and continued to be progression-free for >15 months. Eleven patients (39%) had stable disease that lasted >3 months, including 8 patients who had tumor shrinkage. In total, 6 patients (21%) remained on the trial, and 5 additional patients continued to be followed for survival. The median follow-up for those 11 patients was 13.5 months (range, 8.3–17.0 months). The median survival had not been reached at the time of the current report. Serious adverse events included fatigue (11%), skin toxicity (11%), and neutropenia (36%).

CONCLUSIONS. LEN demonstrated an antitumor effect in metastatic RCC, as evidenced by durable partial responses. LEN toxicities were manageable. Further studies will be required to assess the overall activity of LEN in patients with metastatic RCC. ***Cancer*** **2006;107:2609–16.** © *2006 American Cancer Society.*

KEYWORDS: Phase II, lenalidomide, renal cell carcinoma, immunomodulators.

Renal cell carcinoma (RCC) is the 10th most common cancer in the United States and accounts for >36,000 new diagnoses and >12,000 deaths annually.[1] One-third of patients with RCC present with metastases.[2] Standard chemotherapy produces dismal response rates of 5%; and, to date, no drug has proven efficient.[3] Biologic therapies, including interleukin 2 (IL-2) and interferon (IFN), carry substantial toxicity, produce 15% response rates, and only 5% of patients achieve long-term remissions.[4,5] Therefore, new investigational agents are warranted in the treatment of metastatic RCC.

Clear cell RCC is the major histologic type of renal cancer. Recent advances in understanding the biology of clear cell RCC suggest that silencing of the *von Hippel–Lindau* gene through mutation or hypermethylation leads to increased levels of hypoxia-induced factor α (HIFα) and subsequent activation of many hypoxia-regulated genes.[6,7] The resulting expression of vascular endothelial growth factor (VEGF), transforming growth factor α (TGF-α), platelet-derived growth factor β (PDGF-β), basic fibroblast growth factor (bFGF). and others results in endothelial cell migration, growth, and tumor angiogenesis.[8–10]

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Consequently, inhibition of the VEGF and PDGF signaling pathways may have antitumor activity. Recently, it was reported that agents like bevacizumab,[11] sunitinib,[12] and sorafenib,[13] which inhibit these pathways, had significant clinical activity in cytokine-refractory RCC.

Thalidomide is a drug that has both immunomodulatory and antiangiogenic properties. It has been demonstrated in murine models that thalidomide reduces the expression of potent angiogenic factors, such as bFGF, VEGF, and tumor necrosis factor α (TNF-α).[14–16] Phase II trials with thalidomide in patients with metastatic RCC produced modest responses with a subset of patients experiencing prolonged progression-free survival.[17,18] Furthermore, analysis of angiogenic markers during treatment showed a significant decrease in TNF-α in 1 study[19] of patients who experienced a clinical benefit from thalidomide, supporting the hypothesis of an antiangiogenic mechanism of this drug.

Lenalidomide (LEN) is a structural analogue of thalidomide that has more potency and fewer nonhematologic side effects.[20] It has been demonstrated that LEN has antiangiogenic activity through the inhibition of bFGF-induced, VEGF-induced, and TNF-α-induced endothelial cell migration, which is caused at least in part by the inhibition of the akt phosphorylation response to bFGF.[21] In addition, LEN stimulates T-cell proliferation and the production of IL-2, IL-10, and IFN-γ; inhibits IL-1-β and IL-6; and modulates IL-12 production.[22] T-cell-derived IL-2 production is achieved at least in part through up-regulation of the transcriptional factor AP1 activity.[23,24]

In Phase II trials with LEN, significant activity was demonstrated in patients with myelodysplastic syndromes (MDS) and multiple myeloma,[25,26] and LEN recently was approved by the U.S. Food and Drug Administration (FDA) for patients who have MDS with a deletion 5q cytogenetic abnormality, as well as for patients with refractory/relapsed multiple myeloma.[26] Based on the susceptibility of RCC to immune and antiangiogenic therapy, coupled with the tolerability and possible potency of LEN, an open-label, Phase II, single-center clinical trial was conducted to determine the efficacy and toxicity of LEN in patients with advanced RCC.

MATERIALS AND METHODS

Patients

This single-center, Phase II trial was conducted between September 2004 and April 2005 and included 28 patients. Eligibility criteria included informed consent, age 18 years or older, histologically or cytologically confirmed RCC, measurable disease with evidence of metastases, prior therapy for RCC with $\leq$1 previous systemic regimen, and an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1. In addition, patients had to have adequate organ and bone marrow function. Prior nephrectomy was not required. Patients were excluded if they had received $\geq$2 prior systemic therapies or if they had brain metastases, ongoing cardiac or pulmonary dysfunction, active hepatitis, or human immunodeficiency virus (HIV) infection. Because it is known that thalidomide is teratogenic, and LEN is an analog of thalidomide, women of childbearing potential and men had to agree to use adequate contraception prior to study entry and for the duration of study participation. The current study was approved by the Institutional Review Board of the Cleveland Clinic Foundation and was performed in accordance with the Declaration of Helsinki.

Pretreatment Evaluation

Baseline evaluations (completed $\leq$28 days after initiating LEN treatment) included a medical history and physical examination; computed tomography (CT) scans of the chest, abdomen, and pelvis; assessment of ECOG PS; a complete blood count with differential; biochemical profile (including serum electrolytes, glucose, creatinine, liver function tests, amylase, and lipase); thyroid-stimulating hormone (TSH); 12-lead electrocardiogram; urinalysis; and a serum or urine pregnancy test. Brain imaging was required if there was a clinical suspicion of central nervous system involvement.

Treatment and Follow-Up Studies

LEN was supplied in 25-mg or 5-mg capsules (Revlimid®; Celgene Corporation, Summit, NJ; Revlimid® is a registered trademark of Celgene Corporation). Patients who met all eligibility criteria received LEN 25 mg per day orally on an outpatient basis without regard to meals. LEN was to be taken daily for 21 days followed by a 7-day rest period (28-day cycle). No routine premedications were taken. Treatment continued until unacceptable adverse events (AEs) or documented disease progression occurred. Patients who were removed from the study were followed every 3 months for survival.

Follow-up studies included a complete blood count and biochemical profile 2 weeks after the start of treatment and prior to each new cycle. Complete physical examinations were performed prior to each cycle. CT scans of the chest, abdomen, and pelvis; urinalysis; and electrocardiograms were repeated every 2 cycles. TSH levels were obtained every 3 months.

Dose Modifications

Patients were evaluated for AEs at each visit using the National Cancer Institute Common Terminology Criteria for AEs (version 3.0). For Grade 3 or 4 toxicity that occurred prior to Day 15 of a cycle and resolved to Grade $\leq$2 in severity prior to Day 21, LEN was continued until Day 21 with a 1-level dose reduction. Subsequent cycles were continued at the new reduced dose level. Similarly, for Grade 3 or 4 toxicity that occurred on or after Day 15 of a cycle, LEN was held for the remainder of the cycle and was reduced by 1 dose level in the subsequent cycle. Dose reduction steps were as follows: Dose Level 1, 20 mg daily for 21 of 28 days; Dose Level 2, 15 mg daily for 21 of 28 days; and Dose Level 3, 10 mg daily for 21 of 28 days.

The criteria for beginning a new course of treatment on the scheduled Day 1 of a new cycle included an absolute neutrophil count (ANC) $\geq$1000/mL, a platelet count $\geq$50,000/mL, and resolution of any other LEN-related AEs to Grade $\leq$2 severity. If these conditions were not met on Day 1 of a new cycle, then the patient was evaluated weekly, and a new cycle of LEN was not initiated until the toxicity had resolved, as described above. Patients who had treatment delays $\geq$3 weeks beyond the planned treatment date or who could not tolerate LEN 10 mg (Dose Level 3) daily were discontinued from the study. Granulocyte-colony stimulating factor (G-CSF) was added prior to dose reductions at the investigator's discretion.

Assessment of Efficacy

All patients were evaluated for response after every 8 weeks of treatment. Response categories were assigned by using the Response Evaluation Criteria in Solid Tumors (RECIST).[27] All patients who achieved a partial response (PR) had confirmatory CT scans obtained 4 to 8 weeks after the criteria for response initially were met. All responses were assessed independently by a second oncologist at our institution.

Statistical Methods

The primary endpoint of the study was the best objective response as defined by RECIST. Secondary endpoints included toxicity, the time to treatment failure (TTF), and overall survival (OS). Sample size for the trial was determined by using a 2-stage design with an initial accrual objective of 14 eligible and evaluable patients. If $\geq$1 or more initial response(s) was observed, then 14 additional patients were to be entered up to a maximum of 28 patients overall. In total, at least 3 objective responses were used as the cut-off level for making a decision regarding the efficacy of LEN in this population. With this design, the overall likelihood of rejecting LEN if it was not active (i.e., $\leq$5% objective response rate) was $\geq$85%, whereas there was at most a 10% chance of rejecting LEN if it had an underlying response potential $\geq$20%.

Response and toxicity were summarized using frequency counts, percentages, and exact 95% confidence intervals (for response). The Fisher exact test was used to compare response outcomes between previously treated patients and untreated patients. The

TABLE 1
Patient and Disease Characteristics

Characteristic	No. of patients (%)
Sex	
Men	19 (68)
Women	9 (32)
Age, y	
Mean ± SD	63.5 ± 9.3
Median	67
Range	42–76
Time from diagnosis to study entry, y	
Mean ± SD	4.7 ± 6.2
Median	1.6
Range	1.6 m–19.9 y
Histology	
Clear cell	22 (79)
Other*	6 (21)
Nuclear grade	
II	7 (25)
III	8 (29)
IV	7 (25)
Unknown	6 (21)
ECOG PS	
0	19 (68)
1	9 (32)
Prior nephrectomy	28 (100)
Prior systemic therapy†	16 (57)
Prior radiotherapy	11 (39)
Involved sites	
Lung	18 (64)
Liver	6 (21)
Bone	6 (21)
Lymph nodes	13 (46)
Other	15 (54)
No. of involved sites	
1	6 (21)
2	9 (32)
3	8 (29)
>3	5 (18)
MSKCC risk group	
Favorable	10 (36)
Intermediate	17 (61)
Unknown	1 (4)

SD indicates standard deviation; ECOG PS, Eastern Cooperative Oncology Group performance status; MSKCC, Memorial Sloan-Kettering Cancer Center.

* Other histologic types included mixed clear cell and papillary (3 patients), chromophobe (1 patient), papillary (1 patient), and clear cell with rhabdoid features (1 patient).

† Prior systemic therapy consisted mostly of biologic agents, including interferon-α, interleukin-2, and interleukin-11. Other agents included suramin, erlotinib, bevacizumab, panitumumab, capecitabine, and 5-fluorouracil.

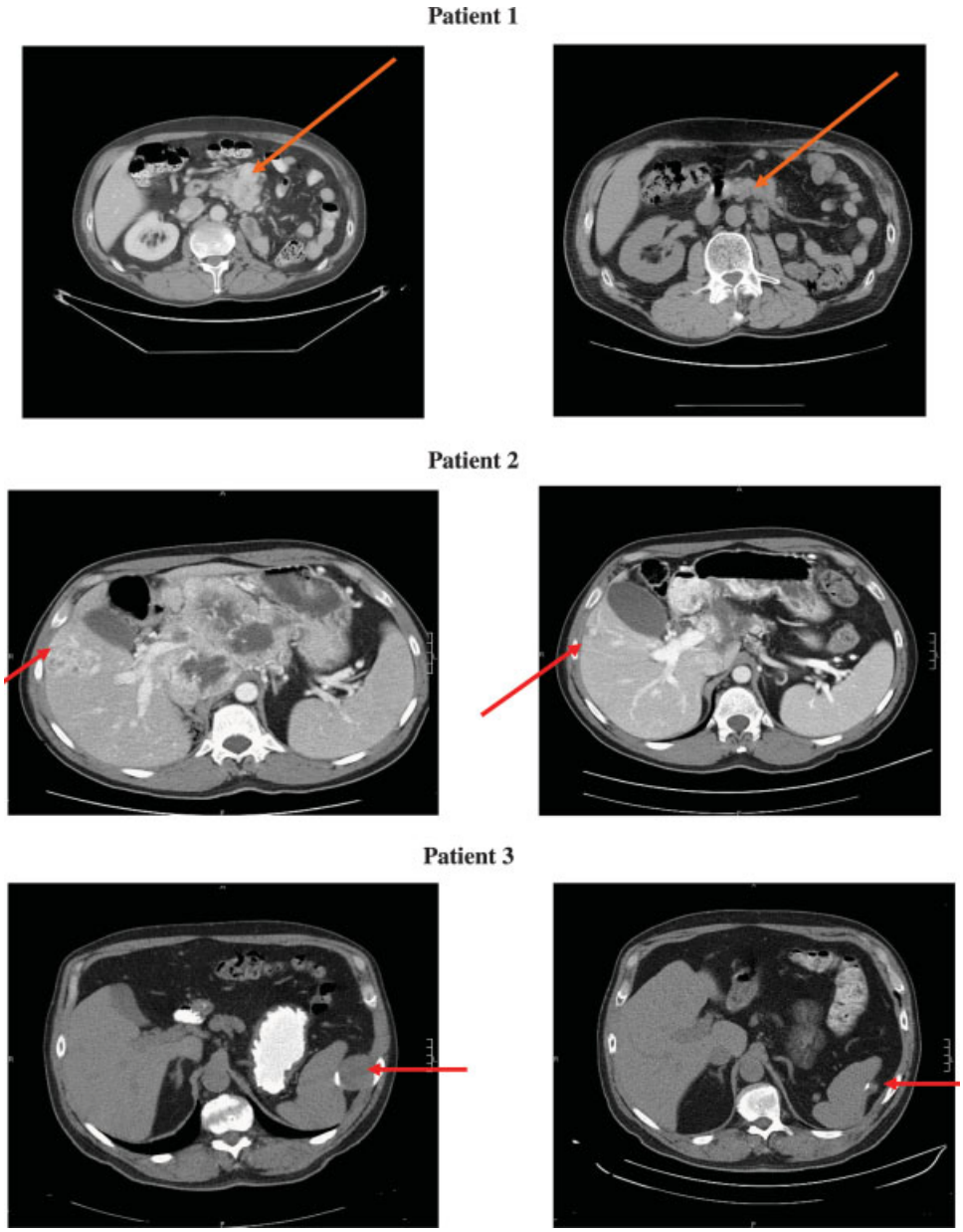

FIGURE 1. These computed tomography scans illustrate responses in Patient 1 (pancreas), Patient 2 (liver), and Patient 3 (parasplenic lymph node).

TTF was measured from the date of study entry to the date that tumor progression was documented or the patient was taken off study for AEs. OS was measured from the date of study entry to the date of death. Survival and TTF were summarized by using the Kaplan–Meier method. The log-rank test was used to compare the TTF in previously treated patients with the TTF in untreated patients.

RESULTS

Patient Characteristics

Twenty-eight patients were treated with LEN, and all were considered eligible and evaluable. After the first 14 patients were entered, 1 of 14 patients achieved a PR, and an additional 14 patients were accrued. Table 1 summarizes patient and disease characteristics. The median age was 67 years, and most patients (68%) had an ECOG PS of 0. All patients had undergone nephrectomy, and 16 of 28 patients (57%) had received prior systemic therapy. The lung was the most common site of metastatic disease (64%). According to the Memorial Sloan-Kettering Cancer Center risk-stratification criteria for untreated patients,[28] 10 patients (36%) had a favorable profile, and 17 patients (61%) had an intermediate profile. Most patients (79%) had clear cell histology.

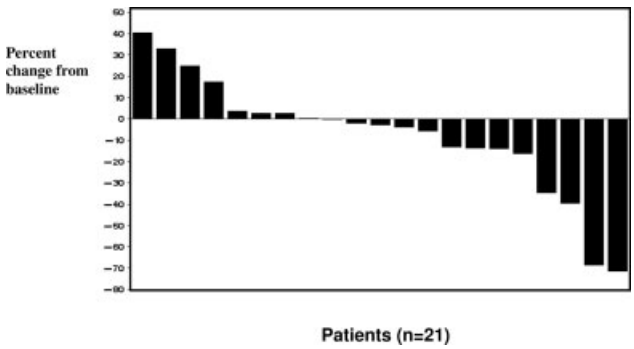

FIGURE 2. This chart illustrates tumor shrinkage in 21 patients who had follow-up imaging studies available.

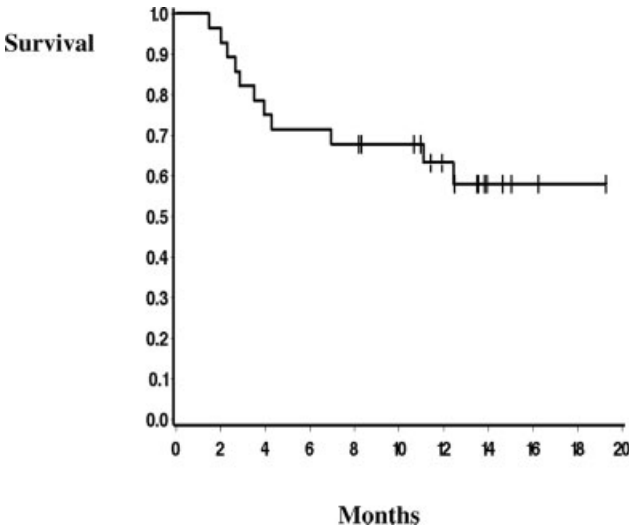

FIGURE 3. This is the overall survival curve for the 28 patients who were treated on the current study.

Clinical Outcome

Twenty-two patients have discontinued therapy, primarily because pf disease progression, and 6 patients continue to be treated. Patients received a median of 4 cycles of treatment (range, from 1 cycle to ≥16 cycles).

No complete responses were noted. Three PRs were observed for an overall response rate of 11% (95% confidence interval, 2–28%). The responses have lasted ≥1.8 months, ≥11.7 months, and ≥11.7 months to date, and all 3 responding patients remained progression-free at a follow-up of ≥15.4 months, ≥15.8 months, and ≥16.9 months, respectively. Responses are illustrated in the pancreas (Fig. 1A,B), liver (Fig. 1C,D), and parasplenic lymph node (Fig. 1E,F).

An additional 11 patients (39%) experienced stable disease (SD) for >3 months, including 8 patients with tumor shrinkage who did not meet the RECIST criteria for a PR. Four of those 11 patients (36%) continued progression-free for >10.1 months, ≥11.3 months, ≥11.9 months, and ≥15.4 months.

Table 1 shows that 16 patients received prior systemic therapy, and 12 patients were untreated. Of the 16 patients who received prior therapy, 2 patients achieved a PR (13%), and 4 had SD for >3 months (25%). One previously untreated patient responded (8%), and 7 patients (58%) had SD that lasted >3 months. The difference in the PR/SD rate was not statistically significant ($P = .25$; Fisher exact test). Regarding patients with nonclear cell histologies, 1 patient with pure chromophobe histology had SD as a best response and continued progression-free for 14 months after the start of therapy. Another patient who had pure papillary type histology progressed after only 1 week on therapy.

Twenty-one patients had at least 1 set of follow-up tumor measurements. Seven patients did not have follow-up tumor measurements because of rapid disease progression (5 patients) or major complications not related to the study drug (2 patients, including 1 patient with a femur fracture and 1 patient with a bowel perforation after surgery). Among those 21 patients, the median degree of tumor shrinkage was 2.9% (range, from −71% to +41%). Figure 2 provides a graphic summary of the maximal degree of tumor shrinkage in these patients. Twelve patients (43%) developed some decrease in tumor size (3 patients who achieved PRs, 8 patients with SD, and 1 patient with progressive disease). The patient with progressive disease developed new subcentimeter lung metastases but continued to respond at the primary target site.

The estimated median TTF for all 28 patients was 3.7 months. The 7 patients who did not have follow-up tumor measurements (rapid progressors) had a median TTF of 3.4 months. The median TTF for previously treated patients was 2.2 months (compared with 4 months for untreated patients; $P = .49$; log-rank test). The estimated 6-month and 12-month failure-free rates were 36% and 29%, respectively.

Survival

The median survival has not been reached. The median follow-up for the 17 patients who remained alive was 13.5 months (range, 8.3–19.3 months). Eleven of 28 patients have died. Their survival curve is plotted in Figure 3.

Toxicity

The most commonly reported AEs were fatigue (86%; severe in 11% of patients), neutropenia (65%; severe in 36% of patients), and skin reactions (68%; severe in 11% of patients) (Table 2). Only 1 patient had neutropenic fever. The median ANC for Cycle 1 was 3600/mL

TABLE 2
Toxicity

	Grade 1/2		Grade 3		Grade 4	
Adverse Event	No. of patients	%	No. of patients	%	No. of patients	%
Treatment-related adverse events						
Fatigue	21	75	3	11	0	0
Skin reactions	16	57	3	11	0	0
Constipation	8	29	0	0	0	0
Diarrhea	8	29	0	0	0	0
Neuropathy	3	11	0	0	0	0
Edema	6	21	1	4	0	0
Nausea/emesis	10	36	0	0	0	0
Thrombosis	0	0	1	4	0	0
Cough/dyspnea	4	14	2	7	0	0
Dizziness	4	14	1	4	0	0
Laboratory abnormalities						
Neutropenia	8	29	7	25	3	11
Thrombocytopenia	13	46	3	11	0	0
Anemia	13	46	3	11	0	0
Electrolytes changes	7	25	2	7	0	0
Increased creatinine	6	21	0	0	0	0
Thyroid function abnormalities	3	11	0	0	0	0
Liver profile abnormalities	5	18	1	4	0	0

(range, 800–9600/mL). After Cycle 1, the median ANC was 1600/mL (range, 300–6700/mL). No patients received G-CSF. Thrombocytopenia occurred in 57% of patients, and 11% of patients had Grade 3 toxicity; no patient developed bleeding or required platelet transfusions.

Three Grade 1 or 2 thyroid function tests (TFTs) were documented. All patients had normal baseline TSH. It is noteworthy that the 3 patients who had Grade 1 or 2 TFTs were the same patients who responded to treatment. The first patient had a TSH level of 0.01 U/mL (normal, 0.4–5 U/mL) with high T3 and T4 levels 6 months after the initiation of LEN. He was asymptomatic, and his TFTs remained abnormal for 5 consecutive months, then normalized, and continued to be normal after an additional 5 months of follow-up and with no thyroid-suppressive therapy. The second patient had Grade 2 hypothyroidism 10 months after she started on LEN. She had an elevated TSH of 179 U/mL (normal, 0.4–5 U/mL), a low T3 of $<$20 ng/dL (normal, 94–170 ng/dL), and low T4 of 0.6 mcg/dL (normal, 5–11 mcg/dl). She noticed a moderate fatigue that did not interfere with her activity of daily living (ADL). She was started on thyroid-replacement therapy and had prompt normalization of her TFTs abnormalities and resolution of her fatigue. The third patient had an elevated TSH of 139 U/mL after 4 months on active therapy. She was mildly symptomatic without restriction in her ADL. Thyroid-replacement therapy was started, and she had rapid correction of her TFTs. One patient developed lower extremity deep vein thrombosis, which was noticed on a follow-up CT scan, and that patient was started on anticoagulation therapy.

There were no treatment-related deaths. Of 25 patients who received $>$1 cycle, 13 patients (52%) required dose modifications. Eight patients had a dose reduction for neutropenia, 1 patient had a dose reduction for neutropenia and anemia, and 4 patients had a dose reduction for other reasons (dizziness, rash, fatigue/anorexia, and anemia/leukopenia).

DISCUSSION

In this Phase II trial, treatment with LEN demonstrated antitumor activity in patients with metastatic RCC, and toxicity was manageable. All responders (11% of all patients) achieved a PR and continued on the trial for $>$15 months without any evidence of disease progression. Eleven patients (39%) had SD that lasted for $>$3 months, including 4 patients (36%) who continued progression-free from 10.1 months to 15.4 months. The duration of the PRs and the tumor shrinkage that was observed in patients who had SD was notable.

Previous Phase II studies with the parent compound, thalidomide, showed responses that ranged between 0% and 17%.[17–19,29–32] Toxicities were common and included constipation, lethargy, thrombosis, and neuropathy.[31] Despite these sometimes troublesome toxicities, the role of thalidomide was explored

in a Phase III trial of previously untreated patients with metastatic RCC in which IFN-α in combination with thalidomide was compared with IFN-α alone.[33] In that trial, there was no difference in response rates, progression free survival, or OS.

Conversely, thalidomide analogues like LEN have greater potency and better tolerability. The most frequent, severe AEs from Phase II trials in patients with multiple myeloma and MDS included fatigue (15%), neutropenia (12%), and rash (6%).[25,26] Unlike thalidomide, side effects like constipation, neuropathy, and sedation were not common.

Rawat et al. published an abstract that described a similar Phase II trial of LEN in 40 patients with advanced RCC. Sixty percent of those patients were treated previously, and all had an ECOG PS of 0. PRs were documented in 7.5% of those patients, and 32.5% were progression free for $\geq$6 months. Those results generally are comparable to those reported here, albeit with shorter follow-up.[34]

The mechanism (s) of action of LEN remains mostly uncharacterized. An antiangiogenic mechanism was proposed through inhibition of endothelial cell migration (as assessed by a wound-healing assay).[35] The same investigators showed in a later report that LEN inhibited the bFGF-induced, VEGF-induced, and TNF-α-induced migration of cell in murine models.[21] It also was shown that LEN increased IL-2 and INF-γ secretion, which augments natural killer cell numbers and function and leads to cancer cell lysis.[36,37]

The observation that only the responders had TFT abnormalities in our trial is noteworthy. In patients with metastatic RCC who are treated with cytokines, it has been suggested that thyroid dysfunction is correlated with a favorable tumor response[38,39] and possibly may be caused by a T-cell-mediated, autoimmune thyroid disease.[40,41] One possibility is that LEN may enhance the immune response to certain autoantigens and to some antigens that are present on tumor cells. In addition, a cross-reaction of thyroid autoimmune responses caused by shared antigens between RCC and thyroid cells may be possible.

Because LEN may have an antiangiogenic mechanism of action, the combination of LEN with new agents, like sunitinib and sorafenib, synergistically may enhance antiangiogenic activity further and may improve overall clinical efficacy. Furthermore, murine models have indicated that VEGF inhibition may be a means of overcoming immune resistance[42,43] and, thus, may enhance the IL-2 antitumor effect that potentially is increased by LEN.

In summary, the results from this study demonstrated that LEN, a thalidomide analogue, has some activity in advanced RCC, because a subset of our patients were progression free for a prolonged period. However, the short TTF in this study prevents us from recommending LEN for clinical use. Future trials with LEN alone, or in combination with novel agents, or in patients who have failed on previous therapies may establish the clinical benefit of LEN in a larger group of patients.

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