A Phase II Trial of Bryostatin-1 for Patients with Metastatic Renal Cell Carcinoma

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BACKGROUND. Patients with metastatic renal cell carcinoma have a poor prognosis and no standard therapy is available. The authors performed a Phase II trial of the novel agent bryostatin-1 in this patient population.

METHODS. In all, 30 patients with measurable, previously untreated metastatic renal cell carcinoma were studied. Patients had excellent physiologic reserve and preserved performance status. Bryostatin-1 (25 $\mu g/m^2$) was given in the PET (polyethyleneglycol, ethanol, and Tween 80) formulation as a 30-minute intravenous infusion on Days 1, 8, and 15 of each 28-day cycle. In general, treatment was continued until disease progression.

RESULTS. Two patients had significant objective responses, although methodologic problems made interpretation difficult. The median time to progression for all patients was 2.1 months; the median overall survival was 13.1 months. The treatment was generally well tolerated. Myalgia was the most common adverse event. One patient died while on study. This was a sudden death for a patient receiving a 15th cycle of therapy. Aside from this patient (for whom the correlation of study drug to death was not clear), no Grade 4 nonhematologic toxicity was encountered in more than 150 treatment courses delivered.

CONCLUSIONS. There is minimal, if any, clinically relevant single-agent activity of bryostatin-1 at this dose and schedule for patients with metastatic renal cell carcinoma. ***Cancer* 2000;89:615–8.** *© 2000 American Cancer Society.*

KEYWORDS: bryostatin, renal cell carcinoma, Phase II, clinical trial.

Despite the introduction of interferon-α, interleukin-2 (IL-2), and combinations of these with cytotoxics, such as fluoropyrimidines, objective response rates in patients with metastatic renal cell carcinoma (RCC) remain low.[1] Improved survival of a treated cohort by virtue of any systemic therapy has not yet been rigorously established, although patients with favorable prognostic features (intact performance status and disease confined to lymph nodes or lung) are reported consistently to have response rates in the range of 30–40%. These responses can be durable: Responding patients have had a median survival of 2–3 years in many reports. Nonetheless, the overall median survival of patients with metastatic RCC remains approximately 1 year. In this context, the testing of new agents, especially those representing novel paradigms, remains a high priority for clinical investigation.

Bryostatin-1 is a novel marine natural product that was reported first in 1982.[2] It has pleotropic effects on myelopoietic cells[3] and was shown in preclinical evaluation to have both antiproliferative activity[4] and differentiating activity.[5] Modulation of cytokines, especially IL-2 signaling, suggested a possible therapeutic role in tumors that were responsive to IL-2 therapy.[6] As a potent compound with a novel

mechanism of action, bryostatin-1 was designated a high priority agent by the National Cancer Institute (NCI).[7] Herein, we report the results of a single-institution Phase II trial of bryostatin-1 in patients with metastatic RCC who had received no prior cytotoxic or immunotherapy for their disease.

MATERIALS AND METHODS

Patient Characteristics

Between June 1996 and July 1998, 30 patients were registered from the Department of Genitourinary Medical Oncology at the University of Texas M. D. Anderson Cancer Center. All patients provided written, informed consent. All registered patients are reported for both toxicity and response.

All patients had histologically confirmed RCC, although biopsy of metastatic sites was not required if histologic confirmation was available for the primary tumor and the presentation was considered typical. All patients had bidimensionally measurable disease (patients with disease confined to bone were not considered measurable). All patients had excellent physiologic reserve. Eligibility criteria included a Zubrod performance status of 0–1, hemoglobin (without transfusion support) $\geq$ 9.5 g/dL, baseline white blood cell count and platelet count in normal range, estimated creatinine clearance of 60 mL per minute, and transaminases $\leq$ 2 times the upper limit of normal. Patients were excluded for any of the following reasons: a known history of human immunodeficiency virus infection, uncontrolled central nervous system metastases, any cerebral vascular event (including TIA) within the previous 6 months, evidence of bifascicular block or i chemia on electrocardiogram or symptoms of arteriosclerosis, or pregnancy, lactation, or inability to practice contraception.

Prior to initiation of systemic therapy, the primary tumor was controlled either by angioinfarction or nephrectomy. This was done to conform to standards of immunotherapy for RCC at the time the trial was initiated. In those patients with the primary tumor still intact at registration, systemic treatment was initiated as soon as patients were fully recovered from the procedure performed to provide local control.

Statistical Considerations

This study was conducted using an optimal two-stage design,[8] looking for a 20% response rate as the threshold of interest. One of 14 patients in the first stage responded, and, thus, accrual was expanded to 30 patients to define the response rate with reasonable confidence intervals.

TABLE 1
Characteristics of Patients at the Time of Protocol Registration

Median age in yrs (range)	58 (38–78)
Gender	
Male	24
Female	6
Zubrod performance status	
0	11
1	17
2	2
Metastatic sites (no. of patients)	
Lymph node	20
Lung	17
Liver	8
Bone	6
Miscellaneous	19
No. of sites	
1	6
2	9
> 2	15
No. of discrete metastatic lesions	
Solitary	3
2–5	6
> 5	21
Control of primary tumor	
Nephrectomy	20
Angioinfarction	10
Laboratory studies: median (range)	
Hemoglobin (g/dL)	13 (10.3–15.8)
LDH (i.u./L)	510 (162–2374; ULN, 618)
Alkaline phosphatase (i.u./L)	115 (53–574; ULN, 126)
Creatinine (mg/dL)	1.3 (0.8–2.2)

LDH: lactose dehydrogenase; ULN: upper limit of normal.

Treatment

All patients were treated according to the dose and schedule set by the NCI on the basis of earlier work, namely, bryostatin-1 at 25 μg/m^2 intravenously (i.v.) over 1 hour on Days 1, 8, and 15 of each 28-day cycle. This was given in the polyethyleneglycol, ethanol, and Tween 80 (PET) formulation, a vehicle consisting of 60% polyethylene glycol 400, 30% ethanol, and 10% Tween 80. All i.v. bags and tubing were non-PVC.

In general, unless unacceptable toxicity was encountered, therapy was continued until progression or "maximum benefit" was achieved, as judged by the treating physician. No objective response was required to continue therapy.

RESULTS

The baseline characteristics of registered patients are summarized in Table 1. Note that, although an eligibility criterion was a Zubrod performance status of 0–1, an audit of the protocol revealed 2 patients who were enrolled with a Zubrod performance status of 2. Most patients had numerous involved sites (Table 1).

Overall, 18 patients (60%) had metastatic sites beyond lymph node or lung. The median number of cycles delivered was 4 (range, 1–14 cycles).

As of February 2000, all patients have either progressed on therapy (21 patients) or have gone off study for other reasons (9 patients); 22 patients have died. The median time to progression for all patients was 2.1 months. The Kaplan–Meier estimate of median survival for all patients was 13.1 months.

Objective tumor regression occurred in two patients. The first patient, a male age 49 years, had a large superior mediastinal mass that was progressive on serial imaging and presumed on clinical grounds to be due to metastatic RCC. This patient went on to have a radiographic complete response. After 12 courses, the patient underwent a superior mediastinal lymph node dissection. No residual malignancy was found. This patient remains free of detectable disease in any site more than 2 years from the initiation of therapy.

A second patient, a female age 69 years with typical, diffuse pulmonary metastases (hundreds of nodules up to 1.5 cm in greatest dimension, diffusely involving both lungs), also had a dramatic regression. However, in this case, bryostatin-1 was started immediately after angioinfarction of the primary tumor; thus, we cannot be sure that this was not a "spontaneous" regression induced by control of the primary tumor. Such cases of remarkable regression after control of the primary tumor are uncommon but well known.[9] This patient completed 6 cycles of therapy and has only two very small (< 1 cm) and radiographically stable nodules remaining by computed tomography evaluation of the chest. Other than these minimal residual abnormalities, this patient has no detectable disease more than 18 months from the initiation of therapy.

In general, toxicity was acceptable, with no Grade 4 nonhematologic adverse events encountered (Table 2). Two patients had Grade 4 lymphopenia that resolved without apparent clinical consequence. As expected from Phase I experience,[10] myalgia was the most commonly encountered adverse event, although this was mild in most cases. Three patients reported significant fatigue that was severe enough in one case to contribute to a decision to discontinue therapy, although the patient did complete 10 months of treatment. Two patients had a novel reaction consisting of generalized "bronzing" of the skin with prolonged exposure to bryostatin-1. This was of no concern to either patient. One additional patient had mild hyperpigmentation that was confined to sun-exposed areas. In all, 3 of 7 patients who were treated for more than 6 months had clinically evident skin changes.

TABLE 2
Summary of Observed Toxicities

Adverse reaction	Grade 1–2	Grade 3	Grade 4
Hematologic			
Anemia	11	2	—
Lymphopenia	1	2	2
Granulocytopenia	1	2	—
Nonhematologic			
Renal toxicity	9	—	—
Myalgia	4	3	—
Fatigue	n/a	3	—
Dyspnea	—	2	—
Dermatitis	—	1	—
Hyperpigmentation	3	—	—

n/a: Not assessed.

One patient died while still on active therapy. This male age 79 years received 14 cycles of bryostatin-1 without incident, maintaining a fully active performance status with clinically stable disease. During the 15th course of therapy, the patient experienced sudden death. This patient had a 30 pack-year smoking history and a remote history of laryngeal carcinoma from which he was apparently cured. In addition, he had mild hypertension for which he took diltiazem, but there was no known history of coronary artery disease. Although some correlation to bryostatin-1 is possible, it seems likely that this was a cardiovascular death that was unrelated to therapy.

DISCUSSION

The optimal systemic treatment for patients with RCC is not known; indeed, to date, no therapy can be considered standard. In the context of this therapeutic deficiency and on the basis of plausibly relevant immunomodulatory effects (and possibly direct cytotoxic effects), we have conducted a Phase II trial of bryostatin-1 at the dose level and schedule set by the NCI. The two major clinical responses observed require some comment. The first patient did not have histologic confirmation of his solitary metastatic site. Because there was no residual tumor in the resected material after systemic treatment, we have no tissue confirmation that this patient had metastatic RCC. However, spread to mediastinal nodes is common (9 of 30 patients in this study had mediastinal lymph node metastases), and it remains our impression that this patient had metastatic RCC. In the second patient, bryostatin-1 was started immediately after angioinfarction of the primary tumor, and the observed response could have been a "spontaneous" regression. Thus, although both of these responses were quite dramatic, neither can be claimed unequivocally to be

due to bryostatin-1. However, even if both of these responses are granted as bona fide treatment-related responses, an objective response rate of 2 of 30 (7%; 95% confidence interval, 1–22%) does not suggest that bryostatin-1 has any role in the treatment of patients with metastatic RCC as a single agent in the dose and schedule that we studied. Moreover, the observed median survival of only 13.1 months was disappointing. For example, a trial of 5-fluorouracil, interferon-α, and IL-2 conducted in the same department with similar eligibility criteria showed a median survival of 22.9 months.[11]

Recently, preliminary data have suggested some promising bryostatin combinations. Thus, despite these disappointing results with bryostatin-1 as a single agent, we do see good reasons to explore combinations of bryostatin-1 with other agents in the treatment of patients with RCC. Clinical studies along these lines already are underway.

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