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A phase II trial of doxorubicin and gemcitabine in renal cell carcinoma with sarcomatoid features: ECOG 8802

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Abstract

Sarcomatoid features can arise in renal cell carcinoma of any subtype and are associated with a poor prognosis. Doxorubicin and gemcitabine in a limited series showed activity in aggressive renal tumors and we wished to formally assess the combination in patients with renal cell carcinoma specifically containing sarcomatoid features. The Eastern Cooperative Oncology Group (ECOG) conducted a phase II trial of doxorubicin 50 mg/m² IV push and gemcitabine 1,500 mg/m² IV over 30 min every 2 weeks in 39 patients with locally advanced or metastatic renal cell carcinoma with sarcomatoid features. Ten patients (26%) had grade 3 toxicity, and four patients (11%) had grade 4 toxicities. Although most toxicity was from myelosuppression, one patient died on study from cardiac dysfunction after a cumulative dose of 450 mg/m² doxorubicin. Six (16%) patients experienced responses (5 partial responses and 1 complete response), and ten (26%) patients had stable disease. In addition, another patient had an unconfirmed partial response and an

additional patient experienced over 50% decrease in her tumor burden after an initial progression. The median overall survival was 8.8 months, and the median progression-free survival was 3.5 months. We conclude that the combination of doxorubicin and gemcitabine, inactive in patients with mostly clear cell histology, demonstrated responses in patients with RCC with sarcomatoid features. We acknowledge the toxicity of this combination but note that limited treatment options exist for this aggressive histology. Only through prospective multicenter trials with comprehensive central pathology review will better treatment options be identified.

Keywords

Sarcomatoid; Gemcitabine; Doxorubicin; Renal cell cancer; Kidney cancer

Introduction

In addition to pathologic stage, tumor size, and Fuhrman nuclear grade, the presence of tumor necrosis and sarcomatoid features are powerful prognostic indicators in renal cell carcinoma [1–6]. Sarcomatoid change is delineated histologically by spindle cell morphology with features similar to those seen in fibrosarcoma or malignant fibrous histiocytoma [7]. Sarcomatoid change is present in 10% of all renal cell carcinomas and can arise alone or in the setting of any of the subtypes (conventional, papillary, chromophobe, collecting duct or unclassified) [7, 8]. The molecular implications of sarcomatoid change are unknown. It has been postulated that the sarcomatoid element represents a histologic consequence of clonal expansions of clear and non-clear cell tumors with progressively more genetic alterations [9]. Clinically, sarcomatoid change in renal cell cancer is characterized by rapid tumor growth and lack of response to cytokine therapy. It carries a poor prognosis with a median survival of 4–6 months in patients with advanced disease [7, 8]. Furthermore, there may be a quantitative relationship between the percentage of sarcomatoid morphology and survival [7, 10].

The rapid growth of tumor associated with this histology suggests that chemotherapy might be able to arrest its growth. Several experiences have supported this approach: Durable and sometimes complete responses have been reported using MAID (mesna, adriamycin, ifosfamide, dacarbazine) (1 patient) chemotherapy [11], gemcitabine, docetaxel and carboplatin (1 patient) and the doxorubicin regimen CYVADIC (2 patients) [12, 13]. Conversely, Escudier reported no responses in 23 patients treated with doxorubicin and ifosfamide [14]. The dose intense regimen of doxorubicin and gemcitabine was first reported by Nanus and Dutcher [15] in a series of patients with sarcomatoid features and aggressive renal cell carcinoma. Of 18 patients, there were two patients with complete responses, five patients with partial responses and two patients with stable disease lasting more than 6 months. Long-term follow-up of 4 of these 18 patients revealed two patients with complete responses of 6 and 8 years, respectively, after starting doxorubicin and gemcitabine, and two patients (rendered complete response by surgery after chemotherapy) surviving 5.5 and 6 years, respectively [16]. We elected to test this regimen formally in a phase II, multicenter cooperative group trial.

Methods

Eligible patients were required to have histologically proven renal cell carcinoma with greater than 75% sarcomatoid change. This criterion was amended in January 2005 to include patients who had histologically proven renal cell carcinoma containing *any* sarcomatoid features. Patients were required to have unresectable recurrent or metastatic disease which was measurable according to solid tumor response criteria (RECIST) version

1.0. Patients must have had no prior therapy for advanced disease, except for radiation therapy which must have been completed at least 4 weeks prior to registration. Patients had to be at least 18 years old, with an ECOG performance status of 0 or 1, and have normal organ function, including adequate bone marrow, liver and renal function (WBC $> 3,000 \text{ mm}^{-3}$ or ANC $> 1,500 \text{ mm}^{-3}$; platelet count $> 100,000 \text{ mm}^{-3}$; bilirubin $< 1.5 \text{ mg/dL}$; SGOT < 2 times institutional upper limit of normal; creatinine $< 2.0 \text{ mg/dL}$). Patients were also required to have normal cardiac function which included a left ventricular ejection fraction (LVEF) greater than the institutional lower limit of normal by radionuclide multi-gated angiogram (MUGA) scan or echocardiogram, and no prior history of myocardial infarction, congestive heart failure or significant ischemic cardiovascular disease within 1 year prior to registration. Patients could have no serious concurrent medical illness or active infection, no current or prior history of brain metastases, and women could not be pregnant or breast-feeding due to the unknown effects of gemcitabine and doxorubicin on an unborn child or nursing infant. Women of childbearing potential and sexually active males were strongly advised to use an accepted and effective method of contraception.

Finally, diagnostic material from the kidney or metastatic site biopsy had to be available for central pathologic review for evaluation by one pathologist. Submission for pathology review of a minimum of one paraffin block and/ or one representative hematoxylin and eosin stained slide and ten unstained slides and a copy of the surgical pathology report were required for patient enrollment. Documentation of TNM parameters (specifically, tumor size, extent of invasion, and presence or absence of vascular invasion, lymph node involvement, metastasis or renal sinus invasion) and tumor characteristics (specifically, non-sarcomatoid histologic subtype, percent sarcomatoid features, Fuhrman grade, and presence or absence of necrosis) were done as part of the central pathology review of these materials. Selected cases were subjected to ancillary studies (immunohistochemistry, for example) as necessary. The percentage of sarcomatoid features was determined by the assessment of all available slides and corroboration with information in the submitted pathology reports.

Study objectives

This was an Institutional Review Board approved cooperative group sponsored phase II open label multi-center trial led by ECOG with the participation of the Southwest Oncology Group (SWOG) and the Cancer and Leukemia Group B (CALGB). The primary objective of the study was to determine the response rate to doxorubicin and gemcitabine in patients with advanced renal cell cancer carcinoma with sarcomatoid features. Secondary objectives were to describe progression-free survival, overall survival, and the toxic effects of doxorubicin and gemcitabine in this patient population.

Treatment administration

After baseline assessment of cardiac function by MUGA or echocardiogram, patients received doxorubicin 50 mg/m^2 IV push and gemcitabine $1,500 \text{ mg/m}^2$ IV over 30 min every 2 weeks (with G-CSF 5 mcg/kg/day , days 2 or 3–10 or pegfilgrastim 6 mg day 2) until disease progression or unacceptable toxicity. The cycle length was 2 weeks. Dose reductions occurred for low granulocytes or platelets, mucositis, cardiac toxicity, or other grade 3–4 toxicities. A repeat MUGA scan or echocardiogram was performed after six doses of doxorubicin (total dose 300 mg/m^2) prior to receiving the next dose of doxorubicin. If the LVEF was below normal for the institution, then the patient continued on gemcitabine alone. If the LVEF was stable, the patient continued to receive doxorubicin at 50 mg/m^2 IV every 2 weeks to a total dose of 450 mg/m^2 . Stable cardiac function was described as no decrease of more than 15% in LVEF by MUGA scan or echocardiogram and no decrease to less than 35% in LVEF by MUGA scan or echocardiogram. It was strongly recommended that patients receiving more than 450 mg/m^2 cumulative dose of doxorubicin be monitored with

MUGA scans or echocardiogram every two cycles thereafter for signs of congestive heart failure.

Assessment of response and toxicity

Radiologic assessment was done by computed tomography or magnetic resonance imaging every 8 weeks (every 4 cycles) and responses were measured according to the RECIST criteria. Toxicities were defined by NCI-CTCAE version 3.0.

Statistical methods

A two-stage design was used for patient accrual. A true population response probability of 20% or greater was of interest, while further testing would not be pursued if the true population response rate was 5% or lower. Initially, 16 patients were accrued (13 patients were assumed to be eligible). Since criteria for continuing (one or more responses) were met, an additional 24 patients were accrued (22 patients were assumed to be eligible). Four or more responses out of the 35 eligible patients would provide evidence for further study of the regimen. This design had a 51% probability of stopping early if the treatment was ineffective, an 8% probability of declaring the treatment effective if it was not (true response rate of 5% or lower), and 90% probability of declaring the treatment effective if the true response rate was 20% or greater. To account for possible ineligible patients a total of 40 patients were accrued.

Descriptive statistics were used to characterize patients at baseline. Exact two stage, two-sided binomial confidence intervals were computed for the response rate. The method of Kaplan and Meier was used to characterize overall survival and progression free survival.

Results

Demographics

Patient characteristics are described in Table 1. From February 2004 to April 2007, 39 patients with renal cell carcinoma with pure sarcomatoid change (47%) or mixed histology containing an identifiable underlying clear or non-clear cell subtype (53%) were registered by ECOG ($n = 35$), NCCTG ($n = 2$) and CALGB ($n = 2$). One patient withdrew before treatment and is excluded from the analyses. Thirty-eight patients were included in the toxicity and response analysis. Most patients had advanced stage tumors (76% were T3 or greater) and metastatic disease at the time of registration.

Treatment toxicity

The side effects of the chemotherapy occurring during or within 30 days of the end of treatment are described (Table 2). Patients received a median of 6.5 cycles (range 1–16). Twenty-three patients (61%) had grade 1 or 2 toxicities, ten patients (26%) had grade 3 toxicities, four patients (11%) had grade 4 toxicities, and one patient died on study. Two types of toxicity predominated: most toxicity was myelosuppression, but the death on study was associated with cardiac dysfunction manifested by a decline in LVEF to 15% after a cumulative dose of 450 mg/m² doxorubicin. The patient completed nine cycles of treatment after which a MUGA scan indicated a LVEF of 38%, decreased from 61% at baseline. The patient's doxorubicin was discontinued but despite supportive treatment the LVEF had declined further to 15%. Four weeks later, the patient died from multi-organ failure. Among the 20 patients with serial MUGA scans, three additional patients had decreases in LVEF of greater than 15% but maintained LVEF greater than 35%. An additional delayed complication occurred in a patient who developed acute myelogenous leukemia after a durable response of 2 years post-treatment (15 cycles).

Treatment efficacy

As shown in Table 3, one complete and five partial responses (PR) were observed (16%, 90% CI 7.1–28.8%). Ten (26%) patients had stable disease. One of these patients had an unconfirmed partial response. Also, one of the patients who initially progressed subsequently had more than a 50% decrease in tumor burden and was alive on the same regimen (off study). The responses are depicted by spider plot in Fig. 1.

For a response to be considered stable, the protocol required that at least one scan be obtained at least 56 days after registration. Four of the unevaluable patients did not have such scans, but did have scans documenting stable disease at intervals of 51–55 days. We note that the patient with the complete response had 100% sarcomatoid features, and three of the five patients with confirmed partial responses as well a patient who initially progressed and then responded to this regimen all had tumors in which sarcomatoid features comprised more than 75% of the RCC (see Table 3). Responses of these patients did not appear to be related to the underlying subtype: one partial response was observed in a patient with non-clear cell (chromophobe) cancer and two patients had a clear cell subtype background.

Two of these three patients are alive without progression (one with a progression-free survival of 2.5 years). One of these patients developed acute myelogenous leukemia after a durable response (2 years) and 15 cycles of treatment and was last reported alive in March of 2008. The third patient was reported alive 20 months after progression. In addition, the patient who initially progressed and subsequently had more than a 50% decrease in tumor burden and was alive on the same regimen (off study) for 16 months.

The median progression-free survival was 3.5 months (95% CI 2.2–5.2 months) and the median overall survival was 8.8 months (6.1–11.1 months) (Figs. 2, 3).

Central pathology review

Available tumor slides from registered patients were identified by review of existing outside pathology report. All available pathology slides were retrieved and reviewed by a single expert (M.P.) at the ECOG Pathology Coordinating Office and Reference Laboratory, Northwestern University in Chicago, who was blinded to patient outcome. The diagnosis of renal cell carcinoma was confirmed on all reviewed cases. The classification of the RCC subtype and presence of sarcomatoid features were based on the 2004 WHO classification of renal tumors. The percentage of sarcomatoid elements in each tumor was estimated by examining every slide from each case individually and calculating the area of the sarcomatoid component relative to the tumor on each slide. The mean percentage of sarcomatoid component relative to the tumor from each slide was added to obtain the total estimated sarcomatoid percentage for each patient. This was not possible in all cases. Documentation of pathological parameters such as percent sarcomatoid features was hindered by limited submission of a representative slide or slides of the primary tumor and the availability of only core biopsy material or metastatic tumor in five cases. This limited review (slides and pathology reports from 19 nephrectomy specimens) showed a median of 80% sarcomatoid features with eight patients showing 100% sarcomatoid features and the remaining 11 patients ranging from 10 to 90% sarcomatoid features. Three patients were confirmed to have sarcomatoid features, but the percentage could not be calculated from the biopsy sample. Fourteen of the cases with percent sarcomatoid features estimated could be classified as clear cell carcinoma with sarcomatoid features, three as chromophobe carcinoma with sarcomatoid features, one as papillary carcinoma (type 2) with sarcomatoid features and one in which the epithelial component could not be subtyped as clear cell, chromophobe or papillary (i.e. “renal cell carcinoma, unclassified”) [17].

Discussion

Sarcomatoid differentiation of renal cancer can be present in different subtypes of RCC and is defined by morphology. The evidence supports that collectively these patients have a poorer outcome and warrant a focused study. Molecular features of the cells that comprise sarcomatoid differentiation have not been extensively characterized. Increased expression of *skp2* was reported in some tumors with sarcomatoid morphology [18]. *Skp2* association with *p27* promotes ubiquitin-mediated degradation, and may plausibly confer a poorer prognosis through this pathway [18]. The *myc* target genes, *Mina 53* and *Ki67*, are also overexpressed in some RCC with sarcomatoid morphology [19, 20]. Increased expression of VEGF, *kit*, *S6* kinase, hypoxia inducible factor 1 alpha, carbonic anhydrase IX, glucose transport protein, and *P53* mutations suggests the importance of angiogenesis [10, 21, 22]. However, others report lower hypoxia inducible factor 1 alpha in renal cell carcinoma with sarcomatoid features, as compared with RCC lacking these features, which suggests that standard anti-angiogenic therapy alone may be less effective [23]. The relationship of these molecular phenotypes to morphology and to response are areas of active investigation further confounded by the fact that sarcomatoid change is present in a variety of RCC subtypes.

In which situations should the combination doxorubicin and gemcitabine be considered?

The combination of doxorubicin and gemcitabine showed encouraging activity. We hoped to analyze whether tumors with a higher percentage of sarcomatoid features respond better to cytotoxic therapy than those with a lower percentage of sarcomatoid features based on one retrospective analysis reporting tumors exhibiting at least 50% sarcomatoid component having an especially poor outcome and another reporting a correlation of amount sarcomatoid component (10 vs. 11–50% vs. more than 50%) with survival [7, 10]. Of the 19 patients whose tumors were reviewed by central pathology (Fig. 4), we note that more responses were seen in patients with a higher percentage of sarcomatoid features. The responses were irrespective of the underlying subtype. There are few published trials focused on RCC with sarcomatoid features. The overall benefit of specific therapies in these patients is based primarily on case reports, retrospective reviews and small prospective trials.

Golshayan et al. [24] retrospectively reviewed the Cleveland Clinics' experience with VEGF-targeted therapy in RCC with sarcomatoid features. A partial response rate of 19% and stable disease rate of 49% was observed in 43 patients, all with prior nephrectomy, and good performance status. However, there were no responses and a 56% stable disease rate in those patients with clear cell histology who had greater than 20% sarcomatoid features on this trial. In those patients with non-clear cell histology, responses to VEGF targeted therapy were confined to those patients with less than 20% sarcomatoid features. These findings contrast with our findings of responses to doxorubicin and gemcitabine in which patients with a higher percentage of sarcomatoid features did respond to therapy. Furthermore, older trials of combination chemotherapy (some inactive in patients with poor risk features or sarcomatoid features) have not reported how many or whether these patients had a predominance of sarcomatoid features [11–14].

Building on these observations, we note that RCC dominated by sarcomatoid change may be fundamentally different from non-sarcomatoid RCC that is traditionally chemo-resistant. Thus, the exploration of chemotherapy, which has cytotoxic properties, in combination with targeted therapy should track this feature and may expand alternatives for these patients in which aggressive growth is a characteristic [25, 26]. The combination of doxorubicin and gemcitabine was tolerable but moderately toxic due to cardiotoxicity and the possible leukemic effect of the anthracycline. In a renal cell carcinoma with a particularly poor prognosis, these side effects must be balanced with the benefit. Combinations of

gemcitabine with tyrosine kinase inhibitors [27–29] that are FDA approved and active in RCC are feasible without much additive toxicity. Through future multicenter prospective trials with rigorous central pathology review using ALL available tumor blocks, there is an opportunity to characterize these combinations in renal cell carcinoma with sarcomatoid features as well as an opportunity to establish which molecular characteristics distinguish the aggressive behavior of these tumors from other kidney cancers.

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Fig. 1.
Spider plot of the percent change in the sum of the longest diameter of target lesions over time in weeks of patients treated on ECOG 8802 trial of doxorubicin and gemcitabine

Fig. 2.
Kaplan Meier plot of the progression-free survival of patients treated on ECOG 8802 trial of doxorubicin and gemcitabine

Fig. 3.
Kaplan Meier plot of the overall survival of patients treated on ECOG 8802 trial of doxorubicin and gemcitabine

Fig. 4.

Bar graph of responses of patients treated on ECOG 8802 trial of doxorubicin and gemcitabine, by categorical breakdown of percent sarcomatoid features on central review (see text)

Table 1

Demographics, including MKCC prognostic features, of patients treated with doxorubicin and gemcitabine on ECOG 8802

	<i>N</i> (%)
Eligible, treated patients	38
Age	
Median (range)	59 (36–77)
Sex	
Male	30 (79%)
Female	8 (21%)
ECOG performance status	
0	19 (50%)
1	19 (50%)
Histologic type per local review	
Sarcomatoid	18 (47%)
Sarcomatoid + clear	13 (34%)
Sarcomatoid + other ^a	7 (18%)
Histologic type of epithelial component per central review	
Clear cell	14 (74%)
Chromophobe	3 (16%)
Papillary, type 2	1 (5%)
Unclassified	1 (5%)
Not assessed/unevaluable	19
Sites of disease	
Bone	10 (26%)
Liver	8 (21%)
Lung	27 (71%)
Lymph nodes	22 (58%)
Other sites	10 (26%)
Prior nephrectomy	33 (87%)
Hemoglobin	
Median (range)	12.2 (7.7–15.1)
Calcium	
Median (range)	9.3 (8.1–12.1)
Lactate dehydrogenase	
Median (range)	177 (75–791)
Months from diagnosis to study entry	
Median (range)	2.0 (0.1–102.6)

^aRhabdoid (two), oncocyte, chromophobe, papillary, spindle cell, granular

Table 2

Grade 3 or higher treatment-related toxicity of patients treated with doxorubicin and gemcitabine (ECOG 8802)

Grade	3	4	5
Hemoglobin	5		
Leukocytes	4		
Neutrophils	4	3	
Platelets	1		
Febrile neutropenia		1	
Infection	3		1
LVEF dysfunction	1		
Dyspnea	1	1	
Fatigue	3		
Death-multiorgan failure			1
Diarrhea	1		
Dysphagia	1		
Stomatitis	2		
Nausea	1		
Chest wall pain	1		
Cough	1		

Table 3

Responses by RECIST criteria of patients treated ECOG 8802 trial of doxorubicin and gemcitabine and the number of responses according to the percentage of sarcomatoid features by central review

Best overall response	N (%)	75% Sarcomatoid features	<75% Sarcomatoid features	Sarcomatoid features unknown
Complete (CR)	1 (3)	1	0	0
Partial response (PR)	5 (13)	2	2	1
Stable (SD) ^a	10 (26)	3	2	5
Progression (PD)	13 (35)	4	2	7
Unevaluable for response ^b	9 (24)	1	2	6

Three of these four patients had pathology reviewed centrally

^aFor at least 56 days. Includes 1 unconfirmed PR

^bIncludes 4 patients with stable disease for 51–55 days