Phase II trial of pegylated-liposomal doxorubicin (Doxil™) in renal cell cancer

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Summary

Twelve patients with refractory renal cell cancer were treated on a phase II study of pegylated-liposomal doxorubicin (Doxil™). The initial dose per course was 55 mg/m² every four weeks with dose modification based on mucositis and hand-foot syndrome (the main limiting toxicities). Toxicities were mild and similar to previous reports but dose reduction per the study protocol, which was designed to control the skin and mucosal toxicities, was common. No definite cardiac toxicity was observed. No objective responses were observed in 11 evaluable patients. This study did not demonstrate activity of pegylated-liposomal doxorubicin in renal cell cancer, although it can be given with mild toxicity.

Introduction

Pegylated-liposomal doxorubicin (Doxil™, Cayelx™) is a liposomal formulation of doxorubicin with a different toxicity profile than non-pegylated liposomes [1–3]. Doxil has been reported to accumulate in tumors in patients with breast cancer and Kaposi sarcoma [4,5]. Although many chemotherapy agents have been tried for renal cell cancer, there are no generally accepted regimens that are highly active [6,7]. Because of the theoretical consideration of tumor localization, a report of a response in a phase I study [8], and the generally low toxicity profile of Doxil, we questioned whether it might be a useful agent in the management of renal cell cancer. The current study was designed to examine the toxicity and efficacy of pegylated-liposomal doxorubicin in patients with renal cell cancer.

The main dose-limiting toxicities of Doxil are mucositis and skin toxicity, primarily hand-foot syndrome. The dose-limiting toxicities for this agent can differ significantly among patients. In addition, when given every 28 days, the delayed effects can result in different toxicities during different cycles following the same dose. Because of the potentially complex relationship between the toxicity profile and the dosing regimen, a detailed dose modification scheme incorporating skin and mucosal toxicities was used based on earlier observations.

Materials and methods

Twelve patients with biopsy proven, measurable, locally advanced or metastatic renal cell cancer and a Karnofsky performance status of ≥40% entered this study. All patients met the following criteria: (1) life expectancy of ≥ 2 months, (2) age ≥ 18, (3) granulocyte count ≥ 1,500/ul, (4) platelet count ≥ 100,000/ul, (5) creatinine ≤ 3.0 mg/dl, (6) serum bilirubin < twice normal, (7) no prior malignancy other than curatively resected in situ carcinoma of the cervix or nonmelanoma skin cancer (8) protime < twice normal, (9) no concurrent infection, (10) no history of congestive heart failure, (11) EF ≥ 45% by MUGA scan, (12) no previous chemotherapy or radiotherapy for ≥ 28 days, (13) measurable disease defined as any mass reproducibly measured in two perpendicular dimensions by physical or radiological means. At the time of entry, all patients had the following studies performed: complete blood counts (CBC), differential, electrolytes, BUN, creatinine, AST, alkaline phosphatase, biliru-
bin, PT, PTT, TT, urinalysis, MUGA scan, appropriate imaging studies. Blood counts were done weekly during therapy. Liver function tests, CBC, electrolytes, BUN and creatinine were done on day one of each course. A MUGA scan was also obtained when the patient reached a cumulative anthracycline dose of 500 mg/m², and at least every 3 cycles after reaching a cumulative dose of 500 mg/m². Tumor measurements were recorded at least every three courses. All patients gave written informed consent, and the Institutional Review Board of the University of Minnesota approved the trial.

Pegylated-liposomal doxorubicin (Doxil, Sequus Pharmaceuticals, Inc., Menlo Park, CA) (IND # 48,629) was administered at 55 mg/m² in ~500 ml DSW by intravenous infusion over 2–4 hours at a rate less than 1 mg/min. Subsequent treatments were given over shorter times. Antiemetics were not given prophyactically. The patient returned monthly for evaluation. Courses were repeated every 28 days or longer if needed based on toxicity so that the absolute neutrophil (ANC) and platelet counts were ≥ 1,500/ul, and 100,000/ul, respectively on day one of each course, and skin and mucosal toxicities had resolved (grade 0).

Doses were modified based on hematologic, mucosal, and skin toxicity. If the maximal mucosal and skin toxicities were both 0, and the nadir ANC was ≥ 1,200 and the platelet count ≥ 100,000, the Doxil dose was increased 10% for the next course. The Doxil dose was decreased 10% for a nadir ANC of 600–749 and/or a platelet nadir of 50,001 to 74,999. If the ANC nadir was < 599 and the platelet nadir > 50,000 the Doxil dose was reduced by 25%. If the platelet nadir was less than 50,000, the Doxil dose was decreased by 50%. If the patient experienced symptomatic mucositis, the next dose was held until the mucositis had healed, after which the subsequent dose of Doxil was reduced as follows based on the maximal mucositis experienced: mild soreness, no change in oral intake, no change; painful, changed to soft food, 10% reduction; painful can not eat ≤ 2 days, 15% reduction; painful can not eat > 2 days, 25% reduction; can not eat-needed parenteral or enteral support, 50% reduction. For skin toxicity including hand-foot syndrome, the next dose was held until the pain had resolved, after which the next dose was reduced as follows based on maximal skin toxicity experiences: painful not preventing normal activities, 10% reduction; painful, interfering with walking or preventing normal activities, or can not wear regular clothes, 25% reduction; confinement to bed, 50% reduction. Dose modifications were planned based on renal, hepatic, and neurotoxicity, but were not needed.

Toxicities were graded according to NIH common toxicity criteria. Therapy was given as long as tolerated without evidence of disease progression. Standard response criteria were used in which the sum of the products of the two largest perpendicular diameters of measurable lesions was classified as PD if > 125% of baseline, SD if between 75–125% of baseline, minor response if between 50–75% of baseline, and PR if <50% of baseline but not a CR.

The study was initially designed to be closed if none of the first 15 patients achieved a response, which would allow a 91% chance of detecting a 15% response rate. However, the study was closed after 12 patients due to a change in support for the study.

**Results**

The ages of the patients (8 men and 4 women) ranged from 40 to 68 years (median 56). All patients had failed immunotherapy. The number of cycles of Doxil given per patient ranged from 1 to 9 with a median of 3. A total of 43 cycles were given. One patient developed bowel obstruction from tumor after the first cycle and did not return for follow up, presumably due to progressive disease, and was not evaluable. Four of the 11 patients evaluable for response had SD for 4, 5, 6, and 6 months. No partial or complete responses were observed.

Twelve patients were evaluable for toxicity from the first cycle, and 8 from 2 cycles (Table 1). Following the first course, dose escalation was planned in 3/12 patients, and dose reduction in 1/12 as described in the Methods. Myelosuppression was not prominent. The most significant toxicities were observed in skin and oral mucosa (Table 1). Of the 7 patients who received 3 cycles, 1 received 66.5 mg/m², 1 received 60.5 mg/m², 3 received 55 mg/m², and 2 received 49 mg/m² in the third cycle. Of the 4 patients receiving ≥ 5 cycles, the maximum non-hematological toxicity observed in subsequent cycles was grade 1 mucositis in 2 patients, grade 2 mucositis and skin toxicity in 1 patient, and grade 0 skin or mucosal toxicity in 1 patient. No bleeding complications were observed. Acute nausea was not observed, and antiemetics were not routinely used. In some cases delayed nausea without emesis, fatigue, and anorexia were observed that could have been related to treat-