Activity of Paclitaxel in Advanced or Recurrent Squamous Cell Cancer of the Cervix[1]

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ABSTRACT

Twenty-six patients with squamous cell cancer of the cervix were treated with i.v. paclitaxel, 250 mg/m^2 over 3 h every 21 days. They received steroid, H_1 and H_2 blocker premedications, and granulocyte-colony-stimulating factor (G-CSF) support (5 μg/kg/day). No prior chemotherapy, except as a radiation sensitizer, was allowed. The median age was 50 (range, 36–81) years, and performance status Zubrod was 1 (range, 0–2). Eight (33%) patients had prior surgery, and 22 (92%) had prior radiation therapy. Twenty-four patients were evaluable for response; 2 were later found to be ineligible. Five patients had partial responses (21%; 95% confidence interval, 6–40%), and 14 (58%; 95% confidence interval, 35–78%) had stable disease. The median duration of response was 10 (range, 3–27+) weeks. The responses were within the radiation port (four responses) and outside of it (one response). The median interval from the start of irradiation to the start of paclitaxel in responding patients was 94 weeks, whereas in patients with stable disease it was 68 weeks, and in patients whose disease progressed it was 46 weeks. Eighty-eight percent of the 105 cycles of paclitaxel were administered at a dose of 250 mg/m^2 or higher. Granulocytopenia was brief and noncumulative, with grades 3 and 4 experienced by 5 and 3 patients, respectively. G-CSF was used for a median of 7 (range, 2–14) days/cycle. Anemia was mild, with G_3 noted in 3 patients, and thrombocytopenia was not significant. Infections and musculoskeletal pain were mild and infrequent. Sensory (14 patients G_1 or G_2 and 2 patients G_3) and motor (4 patients G_1 or G_2 and 1 patient G_3) neurotoxicity was noted. There was no significant cardiovascular toxicity. Paclitaxel is active in patients with squamous cell cancer of the cervix and is well tolerated at this dose schedule with G-CSF support.

INTRODUCTION

Over the past four decades, the incidence and mortality rates for uterine cervical carcinoma have decreased in the United States by as much as 70–75% (1). However, cervical cancer remains a significant problem, because it is the most common cancer of women in some developing countries (2). In the United States, it is the seventh most common cancer in women. In 1995, it was estimated that 15,800 new cases were found and 4,800 deaths were caused by cervical cancer (3).

Surgery and radiation therapy are effective in treating most cases of early cervical carcinoma. Accordingly, chemotherapy has traditionally been used for the palliative management of advanced or recurrent disease that may no longer be managed by the other two modalities. Among the chemotherapeutic agents used for cervical cancer, the ones that have demonstrated the most consistent activity as single agents are cisplatin and ifosfamide, with response rates of 21–31% and 33–50% in various dose schedules, respectively (4–6). Irinotecan, a semisynthetic camptothecin analogue, had response rates of 24 and 27% for cervical cancer in two recent reports (7, 8). Lower response rates are generally seen in patients who have had prior chemotherapy. Responses are also decreased in previously irradiated sites. The duration of response with single agents is brief, usually ranging from 4 to 6 months, with survival durations ranging from 6 to 9 months. In the absence of effective systemic therapy, the prognosis for advanced and recurrent disease remains poor.

Paclitaxel is a taxane alkaloid extracted from the pacific yew (*Taxus brevifolia*; Ref. 9), which inhibits tubular disaggregation (10, 11). Several clinical studies have demonstrated the activity of paclitaxel in advanced and refractory solid tumors (12). Particularly interesting have been the reports of a 50% response rate with high-dose paclitaxel (250 mg/m^2) in ovarian cancer (13–15). Furthermore, the activity of paclitaxel in squamous cell cancer of the head and neck (16, 17) and esophagus (18), with response rates of 60–70% and 44%, respectively, has confirmed its therapeutic potential in the squamous cell cancer histological subtype. Accordingly, we performed a multicenter clinical study of paclitaxel in patients with advanced or recurrent squamous cell cancer of the cervix.

MATERIALS AND METHODS

Women 18 years of age or older with measurable, inoperable, recurrent, or metastatic histologically confirmed squamous cell carcinoma of the cervix were eligible. Patients must have had a Zubrod performance status of 0–2 and an expected sur-

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vival of at least 3 months. Four weeks or more must have elapsed since any prior major surgery or radiation therapy (2 months if irradiation to more than 25% of the bone marrow). Chemotherapy, given as a radiation sensitizer only, must have been followed by a minimum of 1 year without evidence of disease. Furthermore, they were required to have an absolute granulocyte count of at least 1,500 cells/μl, platelet count ≥100,000/μl, hemoglobin ≥8.0 g/dl, serum creatinine ≤1.5 mg/dl, total bilirubin <1.0 mg/ml, and aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase ≤2 times the upper limit of normal in the absence of liver metastases by abdominal computed tomographic scan or ≤4 times the upper limit of normal if liver metastases were present. Patients were excluded if they were pregnant, lactating, or of childbearing potential (unless using effective contraception) or had brain or leptomeningeal metastases or symptomatic peripheral neuropathy of grade 2 or higher. Also ineligible were patients with histories of cardiac dysrhythmias requiring medication or pacemaker therapy or significant cardiovascular disease. Patients taking β-blocker drugs, digitalis drugs, verapamil, or diltiazem required cardiology consultation to determine whether these agents could be substituted. If they could not be substituted, then paclitaxel was infused under telemetry monitoring. Patients were entered consecutively into this multicenter Phase II trial without randomization. All patients signed an informed consent form.

All patients received paclitaxel at an initial dose of 250 mg/m^2 given as a 3-h i.v. infusion every 21 days. The dose of paclitaxel could be escalated to 275 mg/m^2 or reduced to 225 or even 200 mg/m^2, depending on the patient's tolerance. All patients were followed for objective and subjective evidence of toxicity. Patients had to receive a minimum of two complete cycles of paclitaxel before being assessed as evaluable for response to therapy. Patients who progressed after the first cycle were also considered evaluable for response. Patients who demonstrated a response were continued in the study for 6 months after achieving a maximal response. Patients whose best response was stable disease could continue until disease progression. Patients were removed from the study if they experienced unacceptable toxicity.

Oral dexamethasone, 20 mg, was provided as premedication 14 and 7 h before the administration of paclitaxel. Cimetidine, 300 mg, and diphenhydramine hydrochloride, 50 mg, were administered i.v. 60 min before the infusion of paclitaxel. Neupogen (G-CSF),[3] 5 μg/kg/day, was administered s.c. 24 h after the cessation of the chemotherapy infusion. It was administered daily from day 2 until day 19 or until the neutrophil count was ≥10,000/μl on a day after the neutrophil nadir. A minimum interval of 24 h was observed between the last dose of G-CSF and the beginning of the chemotherapy infusion.

The paclitaxel dose was escalated if the granulocyte nadir count was greater than 1,500 cells/μl and the platelet count was greater than 100,000/μl. The dose was reduced for symptomatic neutropenia (<500 cells/μl) no longer than 7 days or asymptomatic neutropenia longer than 7 days. A neurological examination was performed before entry into the study, after two cycles, and when the patient went off study. In cases of neurological toxicity, more frequent examinations were performed and dose modification was as follows. Grade 2 or 3 toxicity, which resolved to grade 1 or higher, required a dose decrease of one level, whereas grade 3 neurotoxicity resulted in taking the patient off study. Other nonhematological toxicities, except for cardiovascular and hypersensitivity reactions, allowed an increase by one level if there was grade 0 or 1 toxicity; however, grade 3 or 4 toxicity required a decrease of one level or discontinuation of the treatment. No dose or schedule alterations were made for alopecia. All courses were held pending hematological recovery to granulocytes ≥1,500/μl, platelets ≥100,000/μl, and complete recovery of nonhematological toxicities. Cardiovascular toxicity of any nature was evaluated by a cardiologist. Patients who experienced severe hypersensitivity reactions to paclitaxel could be rechallenged at the discretion of the study chairman. Patients experiencing a delay in chemotherapy of more than 2 weeks, caused by toxicity, had a one dose level decrease, and those on the lowest dose level were removed from the study. All toxicities encountered during the study were evaluated according to the Common Toxicity Criteria of the National Cancer Institute.

In case of hypersensitivity reaction, premedications prior to paclitaxel infusion were administered as follows: dexamethasone, 20 mg i.v. 24, 18, 12, and 6 h prior to paclitaxel; cimetidine, 300 mg i.v. 6 h and 30 min prior to paclitaxel; and diphenhydramine, 50 mg i.v. 6 h and 30 min prior to paclitaxel. Paclitaxel was dissolved in the usual volume but was infused at one-quarter of the original planned rate over the first 6 h. Patients were under close observation for this period. Thereafter, if no reaction had been noted, the rate was increased to the normal infusion speed. However, should severe reactions still occur, the patient would go off study. In patients with no or minimal reactions to this administration of paclitaxel, subsequent courses would be administered according to the above procedure.

Response durations were measured from the time of response (not the beginning of treatment) until evidence of disease progression. The survival duration of patients was measured from the time of entry into the protocol. The major objective of this study was to determine whether paclitaxel was deserving of further investigation in patients with cervical cancer. Gehan (19) has provided a statistical approach for estimating the confidence of observed response rates and levels of rejection error. Clinically, it is important to detect a 20% response rate in this patient population. If none of the first 14 evaluable patients responded, then the treatment would be rejected as being less than 20% effective, with a chance of false rejection error of 5%. If at least one of the first 14 evaluable patients responded (complete or partial response), then an additional 16 patients would be required, for a total of 30 evaluable patients, to estimate the response rate with a SE of no greater than 10%.

RESULTS

Twenty-six women were entered in the protocol (Table 1) and were evaluable for toxicity. Twenty-four were evaluable for response, because two were later found to be ineligible (one had

[3] G-CSF, granulocyte colony-stimulating factor; CI, confidence interval.

Table 1 Patients' characteristics

Eligible patients	24
Evaluability status: evaluable [*n* (%)]	24 (100)
Age, median (range) (yr)	50 (36–81)
Performance status [*n* (%)]	
0	9 (38)
1	8 (33)
2	7 (29)
Histology: squamous carcinoma [*n* (%)]	24 (100)
Prior therapy [*n* (%)]	
None	1 (4)
Chemotherapy (radiosensitizer)	4 (17)
Irradiation	22 (92)
Surgery	8 (33)
Prior chemotherapy [*n* (%)]	
No. of regimens	
0	20 (83)
1	4 (17)
No. of agents	
0	20 (83)
1	3 (13)
2	1 (4)
No prior immunotherapy [*n* (%)]	24 (100)

Table 2 Response of 24 evaluable patients

Response	*n* (%)	95% CI (%)
Partial response	5 (21)	6–40
No change	14 (58)	35–78

prior chemotherapy not as a radiation sensitizer and the other had elevated total bilirubin). The 24 eligible patients had a median age of 50 (range, 36–81) years and a median performance status Zubrod of 1 (range, 0–2). Twenty-two (92%) of the 24 eligible patients received prior radiation therapy; 4 (17%) received chemotherapy as a radiation sensitizer; 8 (33%) had prior surgery; and 1 (4%) had no prior therapy.

There were five partial responses (21%; 95% CI, 6–40%) among 24 evaluable patients (Table 2), whereas 14 (58%; 95% CI, 35–78%) patients had stable disease, and 5 (21%) progressed. The median time to response was 5 (range, 2–27) weeks, and the median duration of response was 10 (range, 3–25+) weeks. All of the responding patients had prior pelvic irradiation. Four of these patients had marker lesions only within the radiation field, all of which responded. The fifth patient's responding lesions were outside of the field. The patients whose disease responded had a median interval since the start of irradiation to the start of paclitaxel of 94 (range, 25–164) weeks, whereas in patients with stable disease, the median interval was 68 (range, 32–1292) weeks, and in patients with progressive disease, the median interval was 46 (range, 11–237) weeks. Six of the 24 eligible patients have died. Among the eligible patients, the median progression-free survival was 14.5 (range, 5–32+) weeks, and the median overall survival was 18+ (range, 6–51+) weeks. The median duration of follow-up has been 32 weeks.

Most (65%) of 105 courses of paclitaxel were administered at a dose of 250 mg/m^2. However, 12 and 23% of the courses were administered at doses of 225 and 275 mg/m^2, respectively.

Table 3 Major toxicities for all 26 treated patients

	Grade			
Toxicity	1	2	3	4
Anemia	7	5	3	0
Granulocytopenia	2	1	5	3
Infection	1	2	0	0
Fatigue	1	5	0	0
Bone pain	0	2	2	0
Myalgia	1	1	0	0
Neuropathy, sensory	8	6	2	0
Neuropathy, motor	2	2	1	0
Stomatitis	1	1	0	0
Nausea alone	9	4	0	0
Vomiting	1	2	2	0
Constipation	2	4	2	0
Dyspnea	0	2	1	0

The granulocytopenia was brief and noncumulative (data not shown). The median nadir granulocyte count was 7,400 (range, 100–76,000) cells/μl. The median day of nadir occurrence was on day 8. Among the three patients whose nadir granulocyte counts were below 500 cells/μl, the median duration of this granulocytopenia was 4 (range, 1–9) days, whereas among the patients whose granulocytes fell below 1,000 cells/μl, the median duration was 4 (range, 2–8) days. The median number of days per cycle of G-CSF use was 7 (range, 2–14). The median nadir hemoglobin level and platelet count were 11.0 (range, 6.8–14.0) g/dl and 326,000 (range, 118,000–889,000) platelets/μl, respectively. The hemoglobin nadir occurred on median day 8 (range, days 1–23). Anemia and thrombocytopenia were not cumulative (data not shown). Infections were mild and infrequent (Table 3), as were musculoskeletal pain and neuropathy. Nausea and vomiting were mild and manageable. Alopecia was universal. There was no significant cardiovascular toxicity.

DISCUSSION

Despite the moderate activity of platinum, ifosfamide, and irinotecan as single agents and the higher activity of polychemotherapy regimens, there is little evidence to date of the lengthening of the survival of patients with cervical cancer relative to treatment with surgery or irradiation without chemotherapy (20). Accordingly, new active drugs to treat patients with squamous cell cancer of the cervix are in critical need.

In this Phase II trial of paclitaxel, 250 mg/m^2 over 3 h every 21 days with G-CSF support, in patients with advanced or recurrent squamous cell cancer of the uterine cervix, we found a 21% objective response rate. Furthermore, 58% of the patients had at least temporary stabilization of their disease with paclitaxel, and only 21% of these patients progressed prior to the third cycle (6 weeks) of therapy. A preliminary report of a Gynecological Oncology Group study of paclitaxel, 170 mg/m^2 over 24 h, in a population of patients with advanced or recurrent squamous cell cancer of the cervix showed an objective response rate of 17%, including 4% complete, and stable disease among 38% of the patients (21).

Clearly, the results of the two studies are similar and confirm that paclitaxel is an active drug in patients with squamous cell cancer. The duration of response, survival, and tox-

icities have not been reported in detail from the Gynecological Oncology Group study thus far. Accordingly, these aspects of the two studies cannot be compared. The dose schedule of paclitaxel, 250 mg/m^2 over 3 h every 21 days with G-CSF support, has proven to be very well tolerated despite the fact that most (92%) of these patients had prior pelvic irradiation. This is confirmed by the fact that most (88%) of the cycles were given at a dose of 250 or 275 mg/m^2. Interestingly, the hematological toxicity has not been cumulative, as also observed in patients with ovarian cancer (22). The nonhematological toxicity has been tolerable as well.

The present dose schedule of paclitaxel with G-CSF support is active and tolerable in patients with advanced and recurrent cancer of the uterine cervix. This study shall continue until 30 evaluable patients are accrued to define more precisely the response rate, duration of response, progression-free survival, overall survival, and toxicity. Paclitaxel is clinically non-cross-resistant with platinum and alkylating agents, as demonstrated in many trials of refractory ovarian cancer (12, 23). The combination of paclitaxel with carboplatin or cisplatin is tolerable and active (23, 24). Accordingly, a trial of paclitaxel with carboplatin or cisplatin would be reasonable in this patient population. Furthermore, paclitaxel may have activity as a radiation sensitizer (25). In view of the above and the good tolerance of this dose schedule in patients who received pelvic irradiation, it may also be reasonable to study concurrent paclitaxel and irradiation in patients with cervical cancer.

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