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An update of a phase II study of paclitaxel in advanced or recurrent squamous cell cancer of the cervix

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Thirty-two evaluable 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 standard premedications and granulocyte colony stimulating factor (G-CSF) support (5 μg/kg/day). Median (range) age was 49 (29–81) years and performance status Zubrod was 1 (0–2). One patient had a complete response and seven patients had a partial response (25%, 95% CI 8–38%). The median survival was 7.3 months. Granulocytopenia was brief and non-cumulative. G-CSF was used for a median (range) of 8 (1–15) days per cycle. In conclusion: paclitaxel is active in patients with squamous cell cancer of the cervix and is well tolerated in this dose schedule with G-CSF support.

Key words: Cervix cancer, granulocyte colony stimulating factor, paclitaxel.

Introduction

Over the past four decades, the incidence and mortality rates for uterine cervical carcinoma have decreased in the US by as much as 70–75%.[1] However, cervical cancer remains a significant problem, as it is the most common cancer of women in some developing countries.[2] In the US, it is the seventh most common cancer in women. In 1995 it is estimated that 15 800 new cases were found and 4800 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 can 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 (CPT-11), a semisynthetic camptothecin analog, had response rates of 24 and 27% for cervical cancer in recent reports.[7–9] Gemcitabine has 11% objective response rate and 64% stable disease with subjective response rate of 64–92%.[10] 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*).[11] It inhibits tubular disaggregation.[12,13] Several clinical studies have demonstrated paclitaxel's activity in advanced and refractory solid tumors.[14] Particularly interesting have been the reports of a 50% response rate with high-dose paclitaxel (250 mg/m^2) in ovarian cancer.[15–17] Furthermore, the activity of paclitaxel in squamous cell cancer of the head and neck[18,19] and esophagus,[20] with response rates of 60–70 and 44%, respectively, has confirmed its potential in squamous cell cancer histologic subtype. Accordingly, we performed a multi-center clinical study of paclitaxel in patients with advanced or recurrent squamous cell cancer of

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the cervix. We reported the preliminary result of this trial previously.[21,22] We present here the update of this study, confirming the activity of paclitaxel in 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 survival 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 at least 1500 cells/μl, platelet count 100 000/μl or greater, hemoglobin 8.0 g/dl or greater, serum creatinine 1.5 mg/dl or less, total bilirubin below 1.0 mg/ml, SGOT/SGPT/alkaline phosphatase two times or less the upper limit of normal in the absence of liver metastases were present. Patients were excluded if they were pregnant, breast feeding or of child-bearing potential (unless using effective contraception), or had brain or leptomeningeal metastases or symptomatic peripheral neuropathy grade 2 or greater. Also ineligible were patients with a history of cardiac dysrhythmias requiring medication or pacemaker therapy, or significant cardiovascular disease. Patients on β-blocker drugs, digitalis drugs, verapamil or diltiazem required cardiology consultation to determine if these agents could be substituted. 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 dosage 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 or reduced to 225 or even 200 mg/m^2. 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 evaluable for response to therapy. Patients who progressed after the first cycle were considered evaluable for response. Patients who demonstrated a response were continued on study for 6 months after achieving maximal response. Patients whose best response was stable disease could continue until disease progression. Patients were removed from study if they experienced unacceptable toxicity.

Premedication was provided as oral dexamethasone (20 mg) 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 [granulocyte colony stimulating factor (G-CSF)] at 5 μg/kg per 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 achievement of neutrophil count of 10 000 μl or greater after recovery from the 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 1500 cells/μl and the platelet count was greater than 100 000 μl. The dose was reduced for symptomatic neutropenia (below 500 cells/μl) no longer than 7 days or asymptomatic neutropenia longer than 7 days. A neurologic examination was performed before entry into the study, after two cycles and when the patient went off study. In cases of neurologic toxicity, more frequent examinations were performed and dose modification was as follows: grade 2 or grade 3 toxicity, which resolved to grade 1 or greater, required a dose decrease of one level while grade 3 neurotoxicity resulted in taking the patient off study. Other non-hematologic toxicity, except for cardiovascular and hyper-sensitivity reactions, allowed an increase by one level if there was grade 0–1 toxicity; however, grade 3–4 toxicity required a decrease of one level or discontinuing of the treatment. No dose schedule alterations were made for alopecia. All courses were held pending hematologic recovery to granulocytes of 1500 μl or greater and platelets to 100 000/μl or greater, and complete recovery of non-hematologic toxicities. Cardiovascular toxicity of any nature was evaluated with 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 greater than 2 weeks, caused by toxicity, had a one dose level decrease and on the lowest dose level were removed from the study. All toxicities encountered during the study were evaluated according to the National Cancer Institute's Common Toxicity Criteria.

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. 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 seen, the rate was increased to the normal infusion speed. However, should severe reactions still develop, the patient would go off study. In patients with no or minimal reactions to this administration of paclitaxel, subsequent courses of it would be administered according to the above procedure.

Response durations were measured from the time of response (not the beginning of treatment) until there was 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 cervix cancer. We used Gehan's two-step statistical design for a phase II study with an initial target response rate of 20%.[23]

Results

Thirty-five women have been entered on the protocol (Table 1). Thirty-two are evaluable for response as one is too early and two were later found to be ineligible (one had prior chemotherapy not as a radiation sensitizer and the other had an elevated total bilirubin). The 33 eligible patients had a median age of 49 years (range 29–81) and a median performance status Zubrod of 1 (range 0–2). Twenty-six (79%) of the 33 eligible patients received prior radiation therapy and four (12%) chemotherapy as a radiation sensitizer, 11 (33%) had prior surgery and five (15%) had no prior therapy.

There were seven partial responses and one complete response for an overall response rate of 25% (95% CI 8–38%) among 32 evaluable patients (Table 2) while 14 (44%; 95% CI 35–62%) patients had stable disease and four (12%) progressed. The median time to response was 5 weeks and duration of response was 2 months (range 1–5). Among the eligible patients the median progression-free survival was 3.5 months (range 1–17+) and the median overall survival was 7.3 months (range 1–22+). Nine patients remain alive.

The majority (61%) of 142 courses of paclitaxel were administered at a dose of 250 mg/m^2. However, 21 and 17% of the courses were administered at a dose of 225 and 275 mg/m^2, respectively. The granulocytopenia was brief and non-cumulative (data not shown). The median nadir granulocyte count was 3168 (range 108–76 000) cells/μl. The median day of nadir was on day 8. The median (range) numbers of days per cycle of G-CSF used was 8 (1–15). The anemia and the thrombocytopenia were not cumulative (data not shown) and generally mild. The infections were mild and infrequent (Table 3), as were the 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

Table 1. Patient characteristcs

Eligible patients	33
Evaluability status	
evaluable	32
inevaluable (too early)	1
Age: median (range)	49 (29–81)
Performance status	
0	10 (30%)
1	15 (46%)
2	8 (24%)
Race	
Asian	1 (3%)
Black	4 (12%)
Hispanic	8 (24%)
White	20 (61%)
Prior therapy	
none	5 (15%)
chemotherapy (radiosensitizer)	4 (12%)
irradiation	26 (79%)
surgery	11 (33%)

Table 2. Response of 32 evaluable patients

Complete and partial response	8 (25%, 95 CI 8–38%)
No change	14 (44%, 95 CI 25–62%)

Table 3. Major toxicities for all 33 eligible treated patients (250 mg/m^2)

Grade	1	2	3	4
Anemia	11	8	6	0
Granulocytopenia	3	3	6	3
Thrombocytopenia	1	0	0	0
Infection	1	4	1	0
Fatigue	5	6	1	0
Bone pain	0	3	1	0
Myalgia	4	1	0	0
Neuropathy sensory	14	8	2	0
Neuropathy motor	4	1	1	0

of polychemotherapy regimens, there is little evidence to date of the lengthening of the survival of patients with cervix cancer treated with chemotherapy compared with surgery or irradiation without chemotherapy.[24] Accordingly, new drugs for patients with squamous cell cancer of the cervix are sought.

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 have found a 25% objective response rate with 3% complete remission and 44% of the patients had at least temporary stabilization of their disease. A preliminary report of a Gynecologic 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.[25]

The results of the two studies are similar and confirm that paclitaxel is an active drug in patients with squamous cell cancer of the cervix. 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 (79%) of these patients had prior pelvic irradiation. Interestingly, the hematologic toxicity has not been commulative, as also observed in patients with ovarian cancer.[26] The non-hematologic toxicity has been tolerable as well.

Conclusion

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. Paclitaxel is clinically non-cross resistant with platinum and alkylating agents, as demonstrated in many trials of refractory ovarian cancer.[14,27] The combination of paclitaxel with carboplatin or cisplatin is tolerable and active.[27,28] Accordingly, a trial of paclitaxel with carboplatin or cisplatin, or ifosfamide or a combination of the three would be reasonable in this patient population. Early reports of paclitaxel with platinum trials indicate an overall response rate of 50–55%,[29,30] while for paclitaxel, platinum and ifosfamide it is 87%.[31] In view of the activity of irinotecan and gemcitabine in cervix cancer, their combination with paclitaxel should be evaluated as well. Furthermore, paclitaxel may have activity as a radiation sensitizer.[32] Accordingly, it may also be reasonable to study concurrent paclitaxel and irradiation in patients with cervix cancer.

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