Int J Clin Oncol (2008) 13:62–65
DOI 10.1007/s10147-007-0731-5

ORIGINAL ARTICLE

Howard D. Homesley · Nathan P. Meltzer
Lucybeth Nieves · Luis Vaccarello
George S. Lowendowski · Al A. Elbendary

A phase II trial of weekly 1-hour paclitaxel as second-line therapy for endometrial and cervical cancer

Received: November 8, 2006 / Accepted: September 26, 2007

Abstract
Background. The efficacy of weekly paclitaxel has not been well characterized in either cervical or endometrial cancer.
Methods. Eligible women had disseminated endometrial or squamous cell cancer of the cervix, one prior chemotherapy regimen, measurable disease, and a Gynecologic Oncology Group (GOG) performance status of 0–2. At entry, all laboratory results were within normal limits. Paclitaxel 80 mg/m^2 was administered by intravenous infusion over 1 h every 7 days. Response served as the endpoint of the trial.
Results. Forty-four patients were registered, and 15 of 16 patients with endometrial cancer and 20 of 28 patients with cervical cancer were evaluable for response. Four of the 15 (26.7%) endometrial cancer patients responded to treatment, with one complete response of 22 weeks and three partial responses. Stable disease was present in 26.7%. Two of the 20 (10%) cervical cancer patients responded to treatment, with one complete response of 25 weeks and one partial response of 14 weeks. Stable disease was present in 35%. Adverse effects were minimal and easily managed with dose adjustments as needed.
Conclusion. Although confirmatory larger trials are needed, weekly paclitaxel appears promising for advanced endometrial carcinoma, and possibly for squamous cell carcinoma of the cervix.

Key words Paclitaxel · Endometrial cancer · Cervical cancer

H.D. Homesley (✉) · N.P. Meltzer · L. Nieves
The Brody School of Medicine of East Carolina University,
2S-12 Brody Medical Sciences Building, Greenville, NC 27834, USA
Tel. + 1-252-744-2408; Fax + 1-252-744-3582
e-mail: homesleyh@ecu.edu

L. Vaccarello · G.S. Lowendowski
Gynecologic Oncology & Pelvic Surgery, Columbus, OH, USA

A.A. Elbendary
St Louis Gynecology and Oncology, St. Louis, MO, USA

Introduction

Chemotherapy is generally reserved for patients with refractory or recurrent endometrial or cervical carcinoma. Recent reports have shown increasing responses to currently available single-agent chemotherapy in cases of both endometrial and cervical carcinomas.[1–7]

Weekly paclitaxel has emerged as a reasonably well-tolerated option in the active management of several malignancies.[8–13] These early clinical trials of the drug were performed using different administration schedules with infusions ranging from 1 to 24 h, doses ranging from 135 to 250 mg/m^2, and treatment ranging from weekly to every 21 days. The toxicity profile was found to be dependent upon dose and schedule, with decreased hematological toxicity reported in shorter infusion schedules.

Therefore, the efficacy of shorter infusion schedules of paclitaxel has been further investigated, and some phase I/II studies have reported that weekly 1-h infusion of paclitaxel at doses of 40 to 100 mg/m^2 yielded low toxicity profiles.[14–17] The most recent studies have shown similar regimens (60–80 mg/m^2 delivered over 1 h) to have an improved therapeutic index and to be reasonably well tolerated.[18–23] In addition, responses have been observed in women with advanced ovarian cancer whose tumors had previously been shown to fail to respond to paclitaxel delivered as a 3-h infusion on the "standard" every-21-day treatment schedule.[17,23]

Because of the potential benefits of weekly paclitaxel compared to other regimens, the activity of weekly paclitaxel was assessed in second-line therapy in patients with disseminated endometrial cancer or squamous cell cervical cancer.

Patients, materials, and methods

All patients had initial histologic diagnosis and presented with persistent or recurrent measurable disease with no more than one prior chemotherapeutic regimen and a Gynecologic Oncology Group (GOG) performance

status (PS) of 0–2. Adequate bone marrow (granulocytes ≥1500/μl, platelets ≥100 000/μl), renal (serum creatinine <2.0 mg/dl), and hepatic (total bilirubin ≤2.0 × normal, aspartate aminotransferase [AST] or alanine aminotransferase [ALT] ≤2.5 × normal) functions were required. All patients had a life expectancy of at least 3 months. Patients provided written informed consent consistent with federal, state, and local requirements, prior to receiving protocol therapy.

Paclitaxel was administered at 7-day intervals intravenously at a dose of 80 mg/m^2 in 250 ml normal saline over 1 h. One cycle consisted of 4 weeks. Patients received prophylactic anti-allergic medication (dexamethasone 20 mg IV, diphenhydramine 50 mg IV push, and an H_2-blocker IV) 30–60 min prior to receiving treatment. Dexamethasone was given during the first course of therapy but not routinely after this. The use of intravenous diuretic therapy was considered for elderly patients and those with a history of cardiac disease.

Patients were assessed for dose modifications prior to each treatment and patients not tolerating at least 60 mg/m^2 dose levels were taken off treatment. Treatment was also discontinued if the WBC count was less than 3000/μl, absolute neutrophil count (ANC) was less than 1500/μl, or platelets were less than 100 000/μl. All nonhematologic toxicity had to be less than grade 1 before additional study medication was given. ECG was performed within 4 weeks of study entry. Treatment delays greater than 2 weeks regardless of reason led to the patient going off the study.

Appropriate prestudy radiographic assessments were used to document tumor size within 4 weeks of study entry and the method used to document the tumor was used consistently for all evaluations. Tumor measurements were obtained every three cycles (12 weeks) and were repeated in 4 weeks to confirm the response.

Eligible patients who received paclitaxel were evaluable for toxicity, and those who received at least 8 weeks of paclitaxel were evaluable for response. Response was defined as follows: *complete response (CR)*, disappearance of all clinical evidence of tumor, determined by two observations no less than 4 weeks apart; *partial response (PR)*, reduction (≥50%) in the sum of the products of measured lesions compared to baseline, determined by two observations no less than 4 weeks apart and without simultaneous increase (≥25%) in the size of any lesion or the appearance of new lesions, while nonmeasurable lesions remained stable or regressed; *stable disease (SD)*, no significant change in disease status for at least 4 weeks, while a lesion may have decreased (≤50%) in the sum of the products of measured lesions or increased (≤25%) in size, but precluded new lesions; *progressive disease (PD)*, increase (≥25%) in the area of any malignant lesion greater than 2 cm^2 or in the sum of the products of the individual lesions in a given organ site. If only one lesion was available for measurement, PD included either an increase (≥50%) in lesions sized at least 2 cm^2 or the appearance of new lesions. Comparison of tumor size was made with the previous smallest measurement in patients who had attained a PR or with baseline measurements in patients with SD or PD.

The primary endpoint was response by measurable disease change. Patients had to receive at least two cycles of therapy to be evaluable for response, unless progression occurred during the first 8 weeks of the trial. Patients without progression whose PS would not allow for 8 weeks of weekly paclitaxel treatment were not considered evaluable for response because of suboptimal drug dosing.

These studies employed a two-stage accrual design. The cervical carcinoma sample size was based upon the premise that a response rate less than or equal to 25% would be of no clinical interest. The design required entry of approximately 28 patients in the first stage of accrual, with additional accrual of as many as 30 if at least seven responses were noted in the first stage. The endometrial carcinoma sample size was based upon the premise that a response rate less than or equal to 10% would be of no clinical interest, while a response rate greater than or equal to 25% would be an indication that further investigation would be warranted. The design required entry of 25 patients in the first stage of accrual, with additional accrual of 15 patients if at least four responses were noted in the first stage.

Results

Between October 1998 and February 2004, 44 patients were enrolled in the study, of whom 9 were judged to be inevaluable for response because they did not receive a minimum of 8 weeks of paclitaxel.

For the 15 endometrial cancer patients enrolled, most (73%) had received monthly carboplatin/paclitaxel for first-line chemotherapy, while 3 (20%) had doxorubicin and cisplatin and 1 (7%) had carboplatin alone.

Four (26.7%) of the 15 endometrial cancer patients responded to treatment, with 1 patient (6.7%) completely responding for 22 weeks and 3 patients (20%) partially responding for a mean duration of 16.6 weeks (range, 8–20 weeks; Table 1). Stable disease (SD) was present in 4 patients (26.7%), with a mean duration of response of 16.3 weeks (range, 12–21 weeks). Seven patients with PD (46.6%) had a mean length of treatment of 14.9 weeks (range, 8–31 weeks).

The cervical cancer patients received as initial therapy for advanced disease, primarily chemoradiation (70%) or radiation alone (30%) for early-stage cancer. For first-line chemotherapy most received cisplatin (70%), while 10% had carboplatin/ paclitaxel and 10% had cisplatin/ paclitaxel.

Table 1. Endometrial carcinoma

Response	*n*	Duration of response (weeks)		
		Percentage	Mean	Range
Complete	1	6.7	22	
Partial	3	20.0	16.6	8–20
Stable	4	26.7	16.3	12–21
Progressive	7	46.6	14.9	8–31
Total	15	100.0		

Table 2. Cervical carcinoma

Response	*n*	Duration of response (weeks)		
		Percentage	Mean	Range
Complete	1	5.0	25	
Partial	1	5.0	14	
Stable	7	35.0	17.4	9–36
Progressive	11	55.0	10.9	3–22
Total	20	100		

Two (10%) of the 20 cervical cancer patients responded to treatment, with 1 completely responding for 25 weeks and 1 patient partially responding for 14 weeks (Table 2) The cervical group had a 35% rate of stabilization, with a mean duration of response of 17.4 weeks (range, 9–36 weeks). Eleven patients with PD had a mean duration of response of 10.9 weeks (range, 3–22 weeks).

Adverse effects were minimal and easily managed with dose adjustments as needed. Because toxicity was managed on a week-to-week basis there was negligible serious grade 3 and grade 4 toxicity reported.

Discussion

Disseminated endometrial and cervical carcinomas continue to challenge clinicians, and optimal management has yet to be established. Second-line chemotherapy rarely leads to substantial response in either of these patient groups and the choice of drug in this situation is dependent upon toxicity and quality-of-life considerations, in addition to efficacy.

Weekly administration of 1-h infusions of paclitaxel (Taxol; Bristol Myers Squibb, Princeton, NJ, USA) has emerged as a highly desirable option in the active management of several malignancies. This regimen originated from early clinical trials of the drug using different administration schedules of 1- to 24-h infusions, with doses ranging from 135 to 250 mg/m^2, every 1 to 3 weeks.[8–13] These early trials suggested that the observed toxicity profile appeared to depend on dose and schedule. Therefore, shorter infusion schedules of paclitaxel have been further investigated, and some phase I/II studies have reported that 1-h infusion of paclitaxel at weekly doses of 40 to 100 mg/m^2 yielded low toxicity profiles with promising efficacy.[14–17] In addition, more recent studies have reported that similar regimens (60–100 mg/m^2 per week) continue to be well tolerated and have an improved therapeutic index even in patients with advanced ovarian, endometrial, and breast cancers.[18,19,21–24]

Several first-line phase II studies of paclitaxel in disseminated endometrial cancer reported overall response rates of up to 30%.[25–27] Two more recent preliminary studies of weekly 1-h paclitaxel infusion in patients with recurrent endometrial cancer have shown response rates of 67% and 75%, but in small numbers (6/9 and 3/4, respectively) of patients.[24,28] Because response in first-line therapy is often double that in second-line therapy, the present series response rate of 26.7% compares favorably with these recent reports.

There have also been recent reports of prolonged progression-free intervals with weekly paclitaxel in advanced cervical cancer.[5,7] In this present series, the patients with recurrent cervical carcinoma had a response rate of 10% (2/20). This result warrants consideration of palliative therapy, perhaps combining paclitaxel with other active agents such as cisplatin, gemcitabine, or vinorelbine.[2–4,6]

For many cancer sites, the prolonged infusion regimens of paclitaxel have been inconvenient for both clinic and patient, while weekly regimens have achieved comparable therapeutic results in less time. The low toxicity profile and short duration of such treatments make this regimen advantageous for outpatient treatment, providing a therapeutic option to better maintain or improve the patient's quality of life during treatment.

In the present second-line study, weekly doses of paclitaxel at 80 mg/m^2 were given to patients with disseminated endometrial carcinoma or squamous cell cervical carcinoma. Although confirmatory larger trials are needed, weekly 1-h paclitaxel administration appears promising for advanced endometrial carcinoma, and possibly for squamous cell carcinoma of the cervix.

Acknowledgments This work was supported in part by a grant from Bristol-Myers Squibb (Princeton, NJ, USA).

References

1. Homesley HD, Blessing JA, Sorosky J, et al. (2005) Phase II trial of liposomal doxorubicin at 40 mg/m^2 every 4 weeks in endometrial carcinoma: a Gynecologic Oncology Group Study. Gynecol Oncol 98:294–298
2. Bonomi P, Blessing JA, Stehman FB, et al. (1985) Randomized trial of three cisplatin dose schedules in squamous-cell carcinoma of the cervix: a Gynecologic Oncology Group study. J Clin Oncol 3:1079–1085
3. Lhomme C, Vermorken JB, Mickiewicz E, et al. (2000) Phase II trial of vinorelbine in patients with advanced and/or recurrent cervical carcinoma: an EORTC Gynaecological Cancer Cooperative Group Study. Eur J Cancer 36:194–199
4. Schilder RJ, Blessing JA, Morgan M, et al. (2000) Evaluation of gemcitabine in patients with squamous cell carcinoma of the cervix: a phase II study of the Gynecologic Oncology Group. Gynecol Oncol 76:204–207
5. Ota S, Sugiyama T, Ushijima K, et al. (2001) Remission of metastatic cervical adenocarcinoma with weekly paclitaxel. Int J Gynecol Cancer 11:167–168
6. Moore DH, Blessing JA, McQuellon RP, et al. (2004) Phase III study of cisplatin with or without paclitaxel in stage IVB, recurrent, or persistent squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. J Clin Oncol 22:3113–3119
7. Terauchi F, Nagashima T, Kobayashi Y, et al. (2005) A pilot study of weekly paclitaxel administration for patients with relapsed cervical cancer after heavy medication. Gan to Kagaku Ryoho (Japanese Journal of Cancer & Chemotherapy) 32:641–644
8. Eisenhauer EA, ten Bokkel Huinink WW, Swenerton KD, et al. (1994) European-Canadian randomized trial of paclitaxel in relapsed ovarian cancer: high dose versus low dose and long versus short infusion. J Clin Oncol 12:2654–2666
9. Greco FA, Hainsworth JD (1994) Paclitaxel (Taxol): phase I/II trial comparing 1 hour infusion schedules. Semin Oncol 21:3–8
10. Schiller JH, Storer B, Tutsch K, et al. (1994) Phase I trial of 3-hour infusion of paclitaxel with or without granulocyte colony-

stimulating factor in patients with advanced cancer. J Clin Oncol 12:241–248
11. Balat O, Kudelka AP, Tunca JC, et al. (1996) Prolonged stabilization of progressive platinum-refractory ovarian cancer with paclitaxel: brief report. Eur J Gynecol Oncol 17:264–266
12. Tsavaris N, Polyzos A, Kosmas C, et al. (1997) A feasibility study of 1 h paclitaxel infusion in patients with solid tumors. Cancer Chemo Pharm Cancer Chemotherapy & Pharmacology 40: 353–357
13. Seidman AD, Hudis CA, Albanel J, et al. (1998) Dose-dense therapy with weekly 1-h paclitaxel infusion in the treatment of metastatic breast cancer. J Clin Oncol 16:3353–3361
14. Klaassen U, Wilke H, Strumberg D, et al. (1996) Phase I study with a weekly 1 h infusion of paclitaxel in heavily pretreated patients with metastatic breast and ovarian cancer. Eur J Cancer 32A:5 47–549
15. Loffler TM, Freund W, Lipke J, et al. (1996) Schedule- and dose-intensified paclitaxel as weekly 1-hour infusion in pretreated solid tumors: results of a phase I/II trial. Semin Oncol 23:32–34
16. Abu-Rustum N, Aghajanian C, Barakat RR, et al. (1997) Salvage weekly paclitaxel in recurrent ovarian cancer. Semin Oncol 24:62–67
17. Fennelly D, Aghajanian C, Shapiro F, et al. (1997) Phase I and pharmacologic study of paclitaxel administered weekly in patients with relapsed ovarian cancer. J Clin Oncol 15:187–192
18. Perez EA, Vogel CL, Irwin DH, et al. (2001) Multicenter phase II trial of weekly paclitaxel in women with metastatic breast cancer. J Clin Oncol 19:4216–4223
19. Markman M, Hall J, Spitz D, et al. (2002) Phase II trial of weekly single-agent paclitaxel in platinum/paclitaxel-refractory ovarian cancer. J Clin Oncol 20:2365–2369
20. Rosenberg P, Andersson H, Boman K, et al. (2002) Randomized trial of single agent paclitaxel given weekly versus every 3 weeks and with per oral versus intravenous steroid premedication to patients with ovarian cancer previously treated with platinum. Acta Oncol 41:418–424
21. Vaughn DJ, Broome CM, Hussain M, et al. (2002) Phase II trial of weekly paclitaxel in patients with previously treated advanced urothelial cancer. J Clin Oncol 20:937–940
22. Boruta DM 2nd, Fowler WC Jr, Gehrig PA, et al. (2003) Weekly paclitaxel infusion as salvage therapy in ovarian cancer. Cancer Invest 21:675–681
23. Markman M, Fowler J (2004) Activity of weekly paclitaxel in patients with advanced endometrial cancer previously treated with both a platinum agent and paclitaxel. Gynecol Oncol 92:180–182
24. Akizuki S, Katsumata N, Yamanaka Y, et al. (2005) Weekly paclitaxel in patients with CAP-resistant advanced or recurrent endometrial carcinoma: a series of four patients. Int J Clin Oncol 10:272–275
25. Ball HG, Blessing JA, Lentz SS, et al. (1996) A phase II trial of paclitaxel in patients with advanced or recurrent adenocarcinoma of the endometrium: a Gynecologic Oncology Group study. Gynecol Oncol 62:278–281
26. Woo HL, Swenerton KD, Hoskins PH (1996) Taxol is active in platinum-resistant endometrial adenocarcinoma. Am J Clin Oncol 19:290–291
27. Lissoni A, Zanetta G, Losa G, et al. (1996) Phase II study of paclitaxel as salvage treatment in advanced endometrial cancer. Ann Oncol 7:861–863
28. Nishio S, Ota S, Sugiyama T, et al. (2003) Weekly 1-h paclitaxel infusion in patients with recurrent endometrial cancer: a preliminary study. In J Clinical Oncol 8:45–48