A Multicenter Phase II Trial of Losoxantrone (DuP-941) in Hormone-refractory Metastatic Prostate Cancer[1]

Susan D. Huan,[2] Ronald B. Natale, David J. Stewart, George P. Sartiano, Philip J. Stella, John D. Roberts, Aston L. Symes, and Michael Finizio

Ottawa Regional Cancer Centre, Ontario Cancer Treatment and Research Foundation and University of Ottawa, Ottawa, Ontario, Canada K1Y 4K7 [S. D. H., D. J. S.]; University of Southern California, Norris Comprehensive Cancer Center, Los Angeles, California 90033 [R. B. N.]; Albany Medical College, Albany, New York 12208 [G. P. S.]; McAuley Cancer Care Center, Ypsilanti, Michigan 48197 [P. J. S.]; Massey Cancer Center, Richmond, Virginia 23298 [J. D. R.]; DuPont Pharma, Mississauga, Ontario, Canada L5K 2P8 [A. L. S.]; and the DuPont Merck Pharmaceutical Company, Wilmington, Delaware 19805 [M. F.]

ABSTRACT

Our purpose in this study was to determine the efficacy and toxicity of losoxantrone (DuP-941), an anthrapyrazole, in patients with metastatic hormone-refractory prostate cancer. Patients with metastatic prostate cancer progressing on androgen ablation therapy without demonstrable antiandrogen withdrawal response were treated with losoxantrone 50 mg/m^2 i.v. bolus every 21 days. All of the patients had elevated serum prostate-specific antigen (PSA) before study entry and had no prior chemotherapy. Forty-three assessable patients were entered. The median age was 70.6 years (range, 53.9–85.9), median Karnofsky performance scale (KPS), 70% (50–90%), and the median serum PSA, 173 μg/liter (12.5–11,140). The median number of courses was 4 (1–9). Five patients (25%) had a partial response as defined by >50% decline in the serum PSA. Two of nine patients with measurable disease had partial responses and three had minor responses. Thirty percent of patients had improvement in KPS and 37% had an improvement in symptoms with decrease in pain and/or decrease in analgesic requirement. Nonhematological grade 3 and 4 toxicities were one each of grade 3 headache, grade 4 hypocalcemia, grade 3 hyperbilirubinemia, and grade 3 dyspnea. Twenty-six patients (60%) had grade 3 or 4 absolute neutropenia. In conclusion, losoxantrone demonstrated a partial biochemical response rate of 25%, response in measurable disease sites in 22%, and improvement in clinical symptoms in one-third of patients. In this study, PSA increase was not necessarily associated with lack of palliative response.

INTRODUCTION

Cytotoxic chemotherapy has modest activity in hormone-refractory prostate cancer (1). Doxorubicin, an anthracycline, given in different dose schedules has response rates ranging from 25 to 84% (2–6), with higher response rates using the National Prostate Cancer Project response criteria. The cumulative cardiotoxicity seen with doxorubicin has limited its use in this elderly population. The formation of superoxides by anthracyclines triggers a series of events that eventually results in the cardiomyopathy. By modifying the anthracenedione nucleus and replacing the carbonyl group with an additional pyrazole group, the anthrapyrazoles are rendered more resistant to enzymatic reduction, which results in decreased generation of superoxides (7). This property has been confirmed in experimental systems and further supported by their protective role against lipid peroxidation (8). Anthrapyrazoles have demonstrated broad spectrum activity in experimental tumor models (9). Their cytotoxicity is mediated through DNA intercalation and the inhibition of topoisomerase II (10).

In a Phase I study of one of the anthrapyrazoles, DuP-937, two of three patients with metastatic prostate cancer treated at the Ottawa Regional Cancer Center demonstrated more than a 50% decline in PSA.[3] One of these patients with measurable disease obtained a partial response, which was reported previously (11). Losoxantrone (DuP-941) was chosen as the anthrapyrazole for this study because of a better safety profile than DuP-937 and the availability of more clinical data from studies in metastatic breast cancer (12, 13). On the basis of the antitumor activity of the related drug, doxorubicin, in prostate cancer, the responses seen with a related anthrapyrazole DuP-937, and the antitumor activity of losoxantrone in different solid tumor models, losoxantrone was deemed as an appropriate candidate drug to explore in metastatic prostate cancer.

MATERIALS AND METHODS

Patients with histologically confirmed prostate cancer with metastatic disease or locally advanced disease who progressed on hormonal therapy were entered into the study. Patients were eligible if they had a KPS of 50–90%, had not received any prior cytotoxic chemotherapy, had adequate renal function (serum creatinine ≤177 μmol/liter), and hepatic function (total bilirubin of <26 μmol/liter). All of the patients had elevated serum PSA of ≥10 μg/liter at study entry. All of the patients were off antiandrogen therapy at least 2 weeks before study

Received 11/3/98; revised 2/10/99; accepted 2/12/99.
The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
[1] Supported by DuPont Merck Pharmaceutical Company.
[2] To whom requests for reprints should be addressed, at Ottawa Regional Cancer Centre, 190 Melrose Avenue, Ottawa, Ontario, Canada K1Y 4K7. Phone: (613) 737-7700; Fax: (613) 247-3511.

[3] The abbreviations used are: PSA, prostate-specific antigen; KPS, Karnofsky performance scale; EORTC, European Organization for Research and Treatment of Cancer.

Table 1 Patient characteristics

Total no. of patients	44
Total no. of evaluable patients	43
Median age	70.6 yr (range, 53.9–85.9)
Median KPS	70% (range, 50%–90%)
Median serum PSA	173 μg/liter (range 12.5–11,140)
Prior radiation	
Yes	26
No	18
No. of prior hormonal manipulations	
1	2
2	30
3 or more	12
Prior orchiectomy	
Yes	19
No	25
Sites of disease	
Bone	41
Prostate	23
Lymph nodes	11
Liver	5
Soft tissue	5
Lung	1
Other	4

entry and were observed for any withdrawal response. An interval of 3 weeks from radiation was required in all of the patients. Patients with a history of congestive heart failure, unstable angina, cardiomyopathy, arrhythmia requiring therapy, myocardial infarction within 12 months of study entry, or a baseline left ventricular ejection fraction of 45% or below by radionuclide ventriculogram were excluded.

Before treatment, all of the patients had a complete history and physical examination, complete blood count, differential count, chemical survey, PSA, chest radiograph, electrocardiogram, left ventricular gated scan, and bone scan. Computerized tomography of the thorax, abdomen, and/or pelvis, and plain radiographs of bony lesions, if applicable, were done for measurement or evaluation of the sites of disease.

As approved by the Institutional Review Boards of participating institutions, written informed consent was obtained from each patient. Patients were treated with losoxantrone 50 mg/m^2 i.v. bolus every 21 days. Patients with less than a PSA rise of 25% from baseline without a worsening of symptoms continued to a maximum of six courses unless there was development of excess toxicity. Weekly complete blood count and differential counts were done. Physical examination, assessment of subjective improvement, creatinine, liver function tests, PSA, and ultrasound of the abdomen (when used to follow disease sites) were done once every 3 weeks; bone radiographs, computerized tomography scan of evaluable or measurable disease were done every 6 weeks, and bone scan was done every 12 weeks. Left ventricular gated scans were performed after the fifth, eighth, and eleventh courses. All of the patients completed the EORTC QLQ-C30 questionnaire (14) at the beginning of the study before any treatment, at the end of the second course, and when they came off study. Toxicities were graded according to the National Cancer Institute-United States adult toxicity criteria (15).

Table 2 Change in KPS and symptoms in relation to PSA

PSA response[a]	KPS	Symptoms
PR (9)		
Improved	5	5
No change	3	4
Worse	1	0
SD (15)		
Improved	5	4
No change	10	9
Worse	0	2
PD (19)		
Improved	3	6
No change	9	8
Worse	7	5

[a] PR, partial response; SD, stable disease; PD, progressive disease; number in brackets, number of patients.

Data Analysis and Statistical Considerations. Evaluation of PSA response was done by calculating the percentage decline from baseline value: (*a*) a complete biochemical response was a PSA decline to within normal range; (*b*) partial response was >50% decline in PSA; (*c*) stable disease was <50% decline in PSA and not >25% increase in the PSA from baseline; and (*d*) progressive disease was >25% increase in the PSA. Assessment of clinical response was done using standard criteria, and bone scan results were graded as worse, stable, or improved. The statistical method for analysis of response was based on the method of Fleming (16).

RESULTS

Forty-four patients from five centers in North America were registered on the study between September 1993 and December 1994. One patient was not evaluable for response because of a lack of follow-up data. The median number of courses of losoxantrone was 4 (range, 1–10). The primary efficacy variable for this study was the degree of decrease in the serum PSA from the baseline values, supported by clinical parameters. The secondary efficacy variable looked at subjective responses, as measured by the EORTC QLQ-C30 responses, and clinical response by physicians' assessment of patients' symptom relief, analgesic requirement, weight, and change in the KPS. Patient characteristics are shown in Table 1. All except two patients had bone metastases. All of the patients had prior hormonal therapy, with a median of two different types of hormonal maneuver. Leutinizing hormone-releasing hormone agonists were continued at the discretion of individual investigators.

The median PSA value was 173 μg/liter (range 12.5–11,140). Twenty-one percent had >50% decrease in PSA from baseline, including five who had a >75% decrease. The median duration of biochemical response was 11 weeks (range, 4–22 weeks). Thirty percent of patients had improvement in KPS, and 37% had decrease in pain and/or decrease in analgesic requirement. Nausea and loss of appetite were reported more frequently after course 2 of chemotherapy; however, the change in appetite was less pronounced after course 4, and, on progression, both nausea and anorexia became more frequently observed. The median duration of improvement in KPS and improvement in

Table 3 Toxicities, $n = 43$

	Grades[a]			
	1	2	3	4
Hematological				
Leukopenia	3	8	17	3
Neutropenia	1	3	9	17
Anemia	7	3	2	1
Thrombocytopenia	3	1	0	0
Nonhematological				
Nausea	6	10	0	0
Anorexia	11	0	0	0
Vomiting	5	2	0	0
Diarrhea	5	0	0	0
Stomatitis	4	1	0	0
Cardiotoxicity (□ LVEF[b])	1	7	1	0

[a] Worst reported at anytime during treatment.
[b] Decreased left ventricular ejection fraction.

pain was 12 weeks (range, 3–26 weeks) and 6 weeks (range, 1–23 weeks), respectively. The PSA responses in relation to KPS and symptoms are shown in Table 2. Partial biochemical responders had overall either an improvement or no change in their symptoms or KPS. One patient had a worsening of his KPS from 90% to 80%. In the group with stable response in PSA, only two patients had a worsening of their symptoms. Thirty-two percent of patients who had biochemical progression had improvement in their symptoms and 15.7% improvement in their performance status.

Nine patients had bidimensional measurable disease. There were two partial responses—one in the left supraclavicular nodes and the other in the liver. Three patients had minor responses: 44, 47, and 47% reduction in liver, retrocrural and subcarinal nodes, and peripheral lymph nodes, respectively. Of the 22 patients who had follow-up bone scan, 27% had improvement in bone scan, which in one-half of these patients was associated with a PSA response of >50% decline. Stable bone scan was observed in 45%. Median survival for patients on this study was 56 weeks (range, 4–87 weeks).

There were no treatment-related deaths. Toxicities are shown in Table 3. Sixty percent of patients had nadir absolute neutrophil counts of $<0.5 \times 10^9$/liter, and 7% experienced grade 3 and 4 anemia. There was no grade 3 or 4 thrombocytopenia. The most common nonhematological toxicity was alopecia in 55% of the patients, followed by nausea (grade 1 and 2) in 36.4% of patients. One patient had transient grade 3 elevation of serum bilirubin, which subsequently resolved with continuation of losoxantrone. One patient developed grade 3 cardiotoxicity, which responded to medical management. The median age of patients who had any decrease in their ejection fraction was 74 years (range, 67–75). The median cumulative dose at which a drop in the ejection fraction of 15% or more was observed by Kaplan-Meier estimate was 400 mg/m^2 of losoxantrone (95% confidence interval, 350–460 mg/m^2).

DISCUSSION

Doxorubicin was one of the earliest cytotoxic agents evaluated in metastatic hormone-refractory prostate cancer (2–6). Its use in this patient population has been limited by its associated cumulative cardiotoxicity. Ways to delay or decrease toxicities of doxorubicin include giving the drug by continuous i.v. infusion rather than by bolus (17), the use of free radical scavengers such as bispiperazinediones (18), and the generation of analogues with less propensity to form superoxide radicals. Anthrapyrazoles are one such class of drugs developed in the hope of averting cardiotoxicity. On the basis of the observation of three partial biochemical responses (PSA decrease of >50% from baseline) and a partial response in measurable disease in one of these patients in a Phase I study conducted through the National Cancer Institute of Canada using DuP-937 (11), it was thought that the activity of anthrapyrazoles needed to be explored further in patients with hormone-refractory metastatic prostate cancer. As more data were available from studies in metastatic breast cancer on losoxantrone, an analogue of DuP-937, losoxantrone, was chosen for this Phase II study.

PSA has become an important surrogate marker for metastatic prostate cancer, a disease that predominantly affects the bones and in which measurement of responses is imprecise. Hence, we chose PSA response as the primary outcome measurement. Change in symptoms such as a decrease in pain and in analgesic requirement, along with changes in weight and performance status, were secondary outcomes. A decline in PSA was observed in one-half of the patients. Twenty-one % had a >50% decline in the PSA.

Mitoxantrone, in combination with prednisone, had an overall palliative response of 36% in metastatic prostrate cancer (19). A more recent randomized study of mitoxantrone plus prednisone *versus* prednisone alone showed a significantly better quality of life for the combined treatment arm (20). In our study, although a decrease in PSA (biochemical partial response or stable disease) was often associated with improvement or stabilization of symptoms and performance status, a PSA increase was not necessarily associated with a lack of palliative responses [47% had no change in KPS, whereas 16% had improvement; and 42% had stable symptoms, whereas 32% reported improvement in their symptoms]. Losoxantrone, as a single agent, resulted in an improvement of symptoms and quality of life in one-third of the patients. This was offset by a small proportion of patients who experienced loss of appetite and nausea while on the chemotherapy. These two symptoms could potentially be attenuated by the concurrent use of steroids. Losoxantrone seems to have palliative activity that is roughly equivalent to that of mitoxantrone.

The treatment of hormone-refractory prostate cancer remains suboptimal. Cytotoxic agents have largely been investigated in the past. As the biology of hormone-refractory prostate cancer continues to unfold, chemotherapy may complement other more innovative modalities. Biological agents, cytokine-directed therapy, differentiating agents, and antiangiogenic agents will be used increasingly. Combinations of the different modalities to target the different mechanisms in the progression of this disease may be warranted.

REFERENCES

1. Eisenberger, M. A., and Abrams, J. S. Chemotherapy for prostatic carcinoma. Semin. Urol., *6:* 303–310, 1988.

2. DeWys, W. D., Bauer, M., Colsky, J., Cooper, R. A., Creech, R., and Carbone, P. P. Comparative trial of adriamycin and 5-fluorouracil in

advanced prostatic cancer—progress report. Cancer Treat. Rep., *61:* 325–328, 1977.

3. Francini, G., Petrioli, R., Manganelli, A., Cintorino, M., Marsili, S., Aquino, A., and Mondillo, S. Weekly chemotherapy in advanced prostate cancer. Br. J. Cancer, *67:* 1430–1436, 1993.

4. Eagan, R. T., Hahn, R. G., and Myers, R. P. Adriamycin (NSC-123127) *versus* 5-fluorouracil (NSC-19893) and cyclophosphamide (NSC-26271) in the treatment of metastatic prostate cancer. Cancer Treat. Rep., *60:* 115–117, 1976.

5. Torti, F. M., Aston, D., Lum, B. L., Kohler, M., Williams, R., Spaulding, J. T., Shortliffe, L., and Freiha, F. S. Weekly doxorubicin in endocrine-refractory carcinoma of the prostate. J. Clin. Oncol., *1:* 477–482, 1983.

6. O'Bryan, R. M., Baker, L. H., Gottlieb, J. F., Rivkin, S. E., Balcerzak, S. P., Grumet, G. N., Salmon, S. E., Moon, T. E., and Hoogstraten, B. Dose response evaluation of adriamycin in human neoplasia. Cancer (Phila.), *39:* 1940–1948, 1977.

7. Gogas, H., and Mansi, J. L. The anthrapyrazoles. Cancer Treat. Rev., *21:* 541–552, 1996.

8. Frank, P., and Novak, R. F. Effects of anthrapyrazole antineoplastic agents on lipid peroxidation. Biochem. Biophys. Res. Commun., *140:* 797–807, 1986.

9. Graham, M. A., Newell, D. R., Butler, J., Hoey, B., and Patterson, L. H. The effect of the anthrapyrazole antitumour agent CI941 on rat liver microsomes and cytochrome P-450 reductase mediated free radical processes. Biochem. Pharmacol., *36:* 3345–3351, 1987.

10. Leteurtre, F., Kohlhagen, G., Paull, K. D., and Pommier, Y. Topoisomerase II inhibition and cytotoxicity of the anthrapyrazoles DuP 937 and DuP 941 (losoxantrone) in the National Cancer Institute Preclinical Antitumor Drug Discovery Screen. J. Natl. Cancer Inst., *86:* 1239–1244, 1994.

11. Bélanger, K., Jolivet, J., Maroun, J., Stewart, D., Grillo-Lopez, A., Whitfield, L., Wainman, N., and Eisenhauer, E. Phase I pharmacokinetic study of DUP-937, a new anthrapyrazole. Investig. New Drugs, *11:* 301–308, 1993.

12. Talbot, D. C., Smith, I. E., Mansi, J. L., Judson, I., Calvert, A. H., and Ashley, S. E. Anthrapyrazole CI941: a highly active new agent in the treatment of advanced breast cancer. J. Clin. Oncol., *9:* 2141–2147, 1991.

13. Vandenberg, T., ten Bokkel Huinink, W., Hedley, D., Panasci, L., Verma, S., Calvert, H., Francher, D., Azarnia, N., Sisk, R., and Symes, A. A Phase II study of DUP941 in advanced breast cancer patients with no prior chemotherapy. Cancer Investig., *12* (Suppl. 1)*:* 13–14, 1994.

14. Aaronson, N. K., Ahmedzai, S., Bergman, B., Bullinger, M., Cull, A., Duez, N. J., Filiberti, A., Flechtner, H., Fleishman, S. B., de Haes, J. C. J. M., Kaasa, S., Klee, M., Osoba, D., Razavi, D., Rofe, P. B., Schraub, S., Sneeuw, K., Sullivan, M., and Takeda, F. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality of life instrument for use in international trials in oncology. J. Natl. Cancer Inst., *85:* 365–376, 1993.

15. Toxicity Criteria Reference. Modification of the February 1988 recommendations of representatives of the National Cancer Institute's clinical cooperative groups and the cancer treatment evaluation program. NCI, NIH, DHHS, 1998.

16. Fleming, T. One-sample multiple testing procedure for Phase II clinical trials: Biometrics, *38:* 143–151, 1982.

17. Legha, S. S., Benjamin, R. S., Mackay, B., Ewer, M., Wallace, S., Valdivieso, M., Rasmussen, S. L., Blumenschein, G. R., and Freireich, E. J. Reduction of doxorubicin cardiotoxicity by prolonged continuous intravenous infusion. Ann. Intern. Med., *96:* 133–139, 1982.

18. Speyer, J. L., Green, M. D., Zeleniuch-Jacquotte, A., Wernz, J. C., Rey, M., Sanger, J., Kramer, E., Ferrans, V., Hochster, H., Meyers, M., Blum, R. H., Feit, F., Attubato, M., Burrows, W., and Muggia, F. M. ICRF-187 permits longer treatment with doxorubicin in women with breast cancer. J. Clin. Oncol., *10:* 117–127, 1992.

19. Moore, M. J., Osoba, D., Murphy, K., Tannock, I. F., Armitage, A., Findlay, B., Coppin, C., Neville, A., Venner, P., and Wilson, J. Use of palliative end points to evaluate the effects of mitoxantrone and low-dose prednisone in patients with hormonally resistant prostate cancer. J. Clin. Oncol., *12:* 689–694, 1994.

20. Tannock, I. F., Osoba, D., Stockler, M. R., Ernst, D. S., Neville, A. J., Moore, M. J., Armitage, G. R., Wilson, J. J., Venner, P. M., Coppin, C. M. L., and Murphy, K. C. Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative end points. J. Clin. Oncol., *14:* 1756–1764, 1996.

Clinical Cancer Research

A Multicenter Phase II Trial of Losoxantrone (DuP-941) in Hormone-refractory Metastatic Prostate Cancer

Susan D. Huan, Ronald B. Natale, David J. Stewart, et al.

Clin Cancer Res 2000;6:1333-1336.