REVIEW ARTICLE

Drugs 1999; 58 Suppl. 3: 127-131
0012-6667/99/0003-0127/$02.50/0

Oral Chemotherapy in the Treatment of Hormone-Refractory Prostate Cancer

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Abstract

Oral chemotherapy has become a major component of the treatment of advanced prostate cancer. The recognition that prostate cancer grows very slowly and must be treated continuously with active agents has led to the development of several therapeutic regimens. These regimens employ oral agents such as estramustine, cyclophosphamide, and etoposide, as they can be taken on a daily basis at home by the patients. These regimens have demonstrated activity in patients with hormone-refractory prostate cancer; declines in both prostate specific antigen and soft tissue lesions have been demonstrated.

Prostate cancer remains the second leading cause of cancer mortality in males, with an estimated 41 800 deaths in 1997.[1] During the last 4 years, the approach to prostate cancer treatment has been refocused, given the sobering experience with antiproliferative agents over the last 2 decades. New molecular targets are now being explored. Our understanding of the biology of prostate cancer has grown tremendously during the last decade, and these laboratory advances are beginning to be applied successfully in the clinic. Cellular structures, such as microtubules and the nuclear matrix, are potential targets in the treatment of prostate cancer. However, another strategy that has helped to increase the response rate in advanced prostate cancer is the recognition that prostate cancer grows slowly and that, even in fast-growing tumours, only a small percentage of cells (<5%) are in S phase and susceptible to chemotherapy at any given time.[2,3]

1. Estramustine and Etoposide

One successful strategy for the treatment of hormone-refractory prostate cancer has been to target the nuclear matrix using oral estramustine and etoposide. Estramustine phosphate, a combination of estradiol and nitrogen mustard, has been shown to have modest single agent activity against prostate cancer.[4,5] The cytotoxicity of estramustine is exerted through multiple mechanisms. One of the primary mechanisms is believed to be through binding to the nuclear matrix.[6] The nuclear matrix is the RNA-protein network that provides structural support for the nucleus and plays an important role in DNA replication and gene expression.[7,8]

Etoposide, a podophyllotoxin, has demonstrated minimal activity as a single agent against prostate cancer.[9-11] The drug is believed to exert its antineoplastic effect through inhibition of topoisomerase II, an enzyme that plays a critical role in the regulation of DNA structure and replication.[12] Topoisomerase II has been localised to the nuclear matrix.[13]

The interaction of estramustine and etoposide, which exert their effects through the nuclear matrix, has been studied.[14] *In vitro*, a combination of these 2 drugs showed enhanced cytotoxicity and impaired DNA synthesis at the level of the nuclear

Table I. Cell structure as a therapeutic target: estramustine and etoposide in hormone-refractory prostate cancer (all regimens administered at 28-day intervals)

Schedule	No. of patients	>50% PSA decline [no. of patients (%)]	Objective response[a] [no. of patients (%)]	Reference
Estramustine/etoposide				
EMP 15 mg/kg, days 1-21 ETP 50 mg/m^2, days 1-21	52	28/52 (54)	9/20 (45)	15
EMP 10 mg/kg, days 1-21 ETP 50 mg/m^2, days 1-21	62	25/62 (40)	8/15 (53)	16
EMP 6 mg/kg, days 1-21 ETP 50 mg/m^2, days 1-21	56	30/56 (54)	15/33 (45)	17
Estramustine/etoposide/paclitaxel				
EMP 600 mg/m^2, days 1-21 ETP 50 mg/m^2, days 1-21 PXL 135 mg/m^2, 3h infusion, day 1	38	24/38 (63)	5/8 (63)	[b]

a Complete or partial responses in patients with bidimensionally measurable disease.

b K. Pienta, unpublished data.

EMP = estramustine phosphate sodium; **ETP** = etoposide; **PSA** = prostate specific antigen; **PXL** = paclitaxel.

matrix. *In vivo*, a combination of the 2 drugs was more effective at suppressing tumour growth than either agent alone.

The synergistic interaction between these 2 agents formed the basis for a phase II trial.[15] Both agents were given orally for 3 weeks with a 1-week rest period. Of the 20 patients with bidimensionally measurable disease, 50% had objective responses: 3 complete and 6 partial (table I). A prostate specific antigen (PSA) decline of >50% from baseline was demonstrated in 55% of patients. Estramustine caused significant nausea in 29% of patients, and 2 patients withdrew secondary to this toxicity. A second trial examined this combination but used a lower dose of estramustine.[16] This trial enrolled 62 patients, and demonstrated a PSA decline of >50% from baseline in 40% of patients and objective partial responses in 8 of 15 (53%) patients with measurable disease. Toxicity was similar to that in the first trial, although the latter regimen was somewhat more tolerable for patients because of less nausea.

A third study utilised an estramustine regimen of one 140mg tablet 3 times daily (approximately 5 to 6 mg/kg/day) and oral etoposide 50 mg/m^2/day as a single dose for 21 of 28 days.[17] This trial enrolled 56 patients, and demonstrated a PSA decline of >50% in 30 patients (54%). 15 of 33 patients (45%) with measurable disease demonstrated complete or partial responses. Median survival for all patients was 13 months. The regimen was well tolerated, although 12 patients developed grade 3 or 4 neutropenia, and estramustine caused grade 3 or 4 nausea in 4 patients.

These 3 phase II studies suggest that an oral regimen of estramustine and etoposide administered for 21 days every 28 days will yield PSA response rates of 40 to 54% and soft tissue response rates of 45 to 53% (table I).

2. Estramustine, Etoposide and Paclitaxel

In addition to its effect on the nuclear matrix, estramustine also affects microtubules. The drug has been shown to promote microtubule disassembly through its interaction with microtubule-associated proteins and tubulin.[18] Estramustine has been tested in combination with other anti-microtubule agents. For example, vinblastine is an agent that has poor single agent activity in prostate cancer, but has demonstrated synergistic activity in combination with estramustine.[19,20] On the basis of this interaction, the combination has been tested in 3 clinical trials.[21-23] Response rates of 14 to 40% were demonstrated for patients with bidimensionally measurable disease. PSA declines of

>50% were found in 48 to 61% of patients. The therapy was well tolerated. One trial demonstrated that patients who experienced a decline in PSA of >50% on 3 separate occasions had significantly prolonged overall and progression-free survival.[21]

Paclitaxel is another agent that achieves its antineoplastic effect through interaction with microtubules. However, instead of promoting microtubule disassembly, paclitaxel inhibits the disassembly of microtubules. The microtubules formed in the presence of paclitaxel are extraordinarily stable and dysfunctional.[24] Paclitaxel has been shown to have a marked cytotoxic effect on prostate cancer cell lines *in vitro*.[25] However, clinical studies of the drug administered as a single agent have demonstrated minimal activity in patients with hormone-refractory prostate cancer.[26] Preclinical studies of the combination of estramustine and paclitaxel have shown synergistic inhibition of prostate cancer cell growth.[27,28]

On the basis of this evidence, a phase II study of this combination was undertaken. In this study, 24 patients with metastatic prostate cancer who had failed initial androgen blockade and anti-androgen withdrawal were treated with the combination of estramustine and paclitaxel.[29] A decrease from baseline PSA of >50% occurred in 69% of patients. Also, 43% of patients (3 of 7) with bidimensionally measurable disease experienced objective partial responses. The toxicity of the combination was not excessive and most patients tolerated the regimen well.

A preliminary analysis of a phase II trial combining all 3 agents (estramustine, etoposide and paclitaxel) showed an improved response rate compared with estramustine and etoposide alone (K. Pienta, unpublished data). Of the 38 patients available for analysis, 63% had a PSA decline of >50% from baseline. Five of 8 patients with measurable disease had objective partial responses (table I). This trial has recently completed accrual and further follow-up will be forthcoming.

3. Cyclophosphamide

The combination of oral cyclophosphamide, diethylstilbestrol, and prednisone was tested in 54 patients with hormone-refractory prostate cancer (table II).[30] All patients had failed combined androgen blockade and had evidence of a rising PSA following anti-androgen withdrawal. Cyclophosphamide was given as a single oral dose of 100 mg/day for 20 days every 30 days. A prednisone dose of 10 mg/day was given for days 1 to 30. Diethylstilbestrol 1 mg/day was given for the entire duration of treatment. A decrease in pretreatment PSA by >50% was demonstrated in 39% of patients; the mean duration of this response was 6 months. Two of 6 patients with measurable disease demonstrated a partial response. This regimen was well tolerated, with 1 patient experiencing a deep venous thrombosis. The combination therefore ap-

Table II. Low dose oral cyclophosphamide in hormone-refractory prostate cancer

Schedule	No. of patients	>50% PSA decline [no. of patients (%)]	Objective response[a] [no. of patients (%)]	Reference
Cyclophosphamide/prednisone/diethylstilbestrol				
CPM 100 mg/day, days 1-20[b] PRED 10 mg/day, days 1-30 DES 1 mg/day, days 1-30	54	21/54 (39)	2/6 (33)	30
Cyclophosphamide/etoposide				
CPM 100mg, days 1-14 ETP 50mg, days 1-14[c]	20	7/20 (35)	-	31

a Complete or partial responses in patients with bidimensionally measurable disease.

b CPM repeated every 30 days.

c Cyclophosphamide/etoposide regimen repeated every 28 days.

CPM = cyclophosphamide; **DES** = diethylstilbestrol; **ETP** = etoposide; **PRED** = prednisone; **PSA** = prostate specific antigen.

pears to be an active, well tolerated regimen for hormone-refractory prostate cancer.

In another study, 20 patients were given cyclophosphamide (100 mg/day for 14 days every 28 days) in conjunction with etoposide 50mg (table II).[31] Seven of 20 patients demonstrated a response, as measured by a decrease in serum PSA of >50% from pretreatment values. Performance status improved in 26% of the patients and bone pain was relieved in 71%. The mean duration of response was 8 months and the median survival was 11 months.

4. Conclusion

Our understanding of the biology of prostate cancer is rapidly advancing. This increase in knowledge has been accompanied by the rapid development of new therapies based on findings from preclinical studies. Such therapies range from new combinations of traditional chemotherapeutic agents to the use of oral agents in a low dose, protracted fashion to treat slowly cycling tumours with a continuous dose of effective chemotherapy. This dual approach of continuous administration plus the development and use of novel agents has led to an increase in response rates for hormone-refractory prostate cancer.

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