Phase II Study of the Oral Cyclophosphamide and Oral Etoposide Combination in Hormone-Refractory Prostate Carcinoma Patients

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BACKGROUND. Hormonotherapy temporarily controls symptoms in 80% of patients with metastatic prostate carcinoma. Once progression occurs, no consensus exists on further therapy. Oral etoposide (VP–16) has shown clinical efficacy in advanced small cell lung carcinoma, breast cancer, germ cell tumors, and lymphomas. A synergistic effect between etoposide and alkylating agents such as estramustine was recently reported. We began a prospective Phase II study of an oral combination of cyclophosphamide (CPM) and VP–16 in patients with hormone-refactory prostate carcinoma (HRPC).

METHODS. Patients were orally treated with CPM (100 mg/day) and VP–16 (50 mg/day) for 14 days every 28 days. Therapy continued until there was evidence of disease progression.

RESULTS. From November, 1992, to February, 1995, 20 patients with HRPC were entered into the study. Patients were eligible if they had an ECOG performance status (PS) of 0 to 2. All of the patients presented with bone metastasis, and 70% presented with bone pain. Seventy-five percent had failed at least two hormonal manipulations. The mean duration of treatment was 5 months (range 2–12). Performance status improved in 26% of the patients, and bone pain was relieved in 71%. An objective response was defined as a decrease of 50% or more in the prostate-specific antigen (PSA) level. One patient demonstrated a complete response, and six patients had partial responses assessed by PSA plasma levels (objective response rate: 35%). The mean duration of response was 8 ± 6 months (range: 2–24). Median survival was 11 months. Toxicities were minimal.

CONCLUSIONS. The combination of oral CPM and VP–16 may be an active and well tolerated regimen for patients with HRPC. ***Cancer* 1996; 77:1144–8.**

KEYWORDS: prostate carcinoma, hormone-refractory status, etoposide, cyclophosphamide.

Prostatic carcinoma is the most common malignancy among elderly men. Treatment of the metastatic cancer with hormone therapy temporarily controls symptoms in 70–80% of patients.[1] Nevertheless, after a remission period, a relapse invariably occurs. After progression, no effective treatment is clearly available, and the median survival is about 6 months in duration.[2] Therefore, progressive metastatic hormone-refractory disease remains a therapeutic challenge. In light of the mechanisms believed to be involved in the development of recurrent disease, vigorous effort is being focused on the identification of nonendocrine treatments. However, therapeutic approaches capable of controlling pain and improving the quality of life without producing major side effects are somewhat restricted. An antitumor response induced by chemotherapy is generally

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TABLE 1
Characteristics of Patients

Characteristics	No. of patients
Metastatic sites	
Bone	20
Liver	1
Paraaortic nodes	7
ECOG PS	
0	5
1	12
2	3
Bone pain	
None	6
Slight	6
Moderate	7
Severe	1
No. of lines of previous HT	
1	5
2	4
3	7
4	4
Previous CT	7

ECOG: Eastern Cooperative Oncology Group; PS: performance status; HT: hormone therapy; CT: chemotherapy.

limited and of short duration, and, because it is not generally tolerated well, chemotherapy is not always feasible in such elderly patients.

Etoposide is a podophyllotoxin derivative that is known to inhibit topoisomerase II at the level of the nuclear matrix.[3] In preclinical studies, Pienta and Lahr[4] demonstrated a significant growth inhibition by etoposide both in human-derived prostate cancer cells and in the Dunning rat prostate carcinoma model. Alkylating agents have shown some clinical efficacy in advanced prostate cancer.[5] Moreover, a few recent Phase II trials have shown promising results of etoposide combined with alkylating agents such as estramustine[6] or cisplatin.[7] We report herein the results of a Phase II study performed between 1992 and 1995 to assess the efficacy of an oral combination of cyclophosphamide and etoposide on progressive metastatic hormone-refractory prostate cancer (HRPC).

PATIENTS AND METHODS

Patient Selection

From November, 1992, through February, 1995, 20 patients with histologically confirmed prostate carcinoma and hormone-refractory status according to The National Prostatic Cancer Project (NPCP) criteria were included in the study. Patients characteristics are listed in Table 1. The ages ranged from 62 years to 81 years (mean 70 ± 5 years). Bone metastases were documented on bone scan before inclusion for all patients. Seven patients presented with a bidimensionally measurable disease (paraaortic nodes in seven patients and liver metastasis in one patient). No patient had hypercalcemia. Seventy-five percent of patients had received two previous hormonal regimens or more. Seven patients (35%) had received chemotherapy excluding etoposide and cyclophosphamide. The Eastern Cooperative Oncology Group (ECOG) performance status (PS) was 0 in 5 patients (25%), 1 in 12 patients (60%) and 2 in 3 patients (15%). One patient complained of dysuria. Altogether 14 patients (70%) presented with bone pain, which was slight in 6 cases, moderate in 7 cases, and severe in 1 case, requiring opioids. The mean interval between metastasis occurrence and inclusion into the study was 24 months (range 1–78 months). All patients had basal prostate-specific antigen (PSA) plasma levels above 20 ng/ml (mean 528 ± 587 ng/ml, range 21–2750 ng/ml) and castration levels in plasma testosterone.

Treatment

Eligible patients were treated orally with cyclophosphamide (100 mg/day) and etoposide (50 mg/day) for 14 consecutive days every 28 days. Treatment was continued until complete remission was achieved and was discontinued in cases of patient refusal, acute life-threatening Grade 3 or 4 toxicities according to WHO criteria, or progression of the disease. Medical castration with luteinizing hormone–releasing hormone (LH–RH) agonists was maintained throughout the study for previously treated patients. Initiation of therapy with antiandrogen or estrogen was not allowed. For four patients, flutamide was stopped 4 weeks before inclusion. Informed consent was obtained from each patient before treatment.

Investigations and Assessments

Patients were assessed before initiation of the treatment and then every month for PS, pain evaluation, urinary symptoms, physical examination, complete blood count, biochemistry, and PSA levels (radioimmunoassays). A bone scan and radiologic investigations were performed at study entry and every 3 months according to the clinical evolution. A complete response was defined as normalization of PSA plasma levels along with the complete disappearance of all clinical and radiologic features. An objective response (OR) was defined as a decrease of 50% or more in the PSA plasma level. A decrease of less than 50% was considered as stabilization. Progression was defined as an increase of 25% or more in PSA plasma levels. The definition of response in PSA plasma levels required reproducibility with a second dosage at a 1 month interval.

Statistical Analysis

Analysis was performed in July, 1995. Survival times were established from the date the patient entered into the

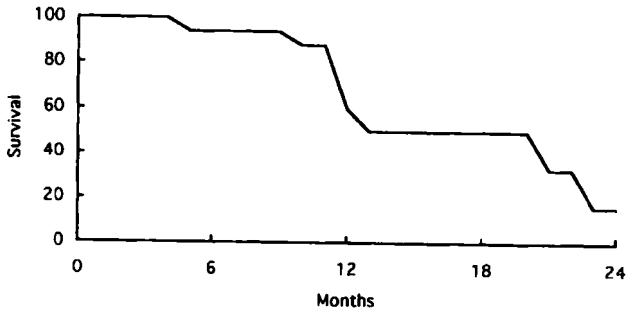

FIGURE 1. Kaplan–Meier overall survival curve for all patients included in the study (N = 20 patients).

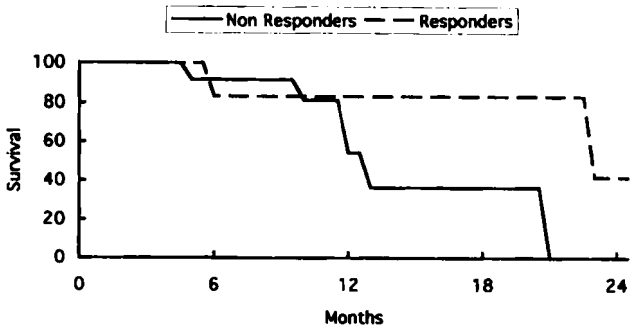

FIGURE 2. Comparison of overall survival between responders (N = 7) and nonresponders (N = 13).

study until the date of death or last follow-up. Survival curves were calculated by the Kaplan–Meier method and compared by log-rank testing.

RESULTS

Twenty patients were included in the study. All patients were evaluable for response and toxicity. The mean duration of treatment was 5 months (range 2–12 months). One patient was withdrawn from the study after two courses of chemotherapy because of the occurrence of severe spinal cord compression.

Response

Among the 15 patients with a basal PS greater than 0, the PS improved in four patients (26%), remained unchanged in ten, and worsened in one. Among the 14 patients who presented with bone pain, this symptom resolved in seven patients, was improved in three (response rate 71%), remained stable in three, and worsened in one. Among the subset of patients without pain at inclusion, one began to experience pain under therapy.

Regarding PSA level, there was one complete response and six partial responses (OR 35%). The mean duration of response was 8 ± 6 months (range 2–24 months). Stabilization was obtained in seven patients (35%). The biologic response was correlated with clinical improvement in all but one patient, who needed radiation therapy for bone metastasis. The patient who achieved a complete response initially presented with PS 2, severe bone pain requiring opioids, a 186 ng/ml PSA plasma level, and multiple hot spots on bone scan. Complete remission was obtained after five courses of treatment and was maintained 24 months later, off treatment for 12 months (PS 0, no pain, no analgesic consumption, 1 ng/ml PSA plasma level, normal bone scan). Two patients with bidimensionally measurable disease presented a partial objective response (durations 6 and 11 months). For one partial responder, flutamide had been stopped 4 weeks before inclusion.

Survival

At the time of analysis, 9 patients were dead, 11 were alive, and 1 was disease-free. As is shown in Figure 1, the 1 year overall survival and the median survival were 60% and 11 months, respectively. The 1 year survival was 82% for responders and 52% for nonresponders (P = 0.18; see Fig. 2). Seventeen patients (85%) received subsequent hormonotherapy or chemotherapy after relapse or progression. Only one showed a transient clinical response.

Tolerance

Toxicities were minimal. Transient WHO Grade I neutropenia, nausea, and alopecia were seen in one, three, and two patients, respectively. Four patients (20%) complained of unusual asthenia.

DISCUSSION

The objective of this study was to evaluate the efficacy of an oral combination of etoposide and cyclophosphamide when administered for 14 days every 28 days in patients with HRPC. The oral route appeared attractive in elderly patients, preserving the best quality of life possible. Treatment was given on an outpatient basis and was well tolerated. No concurrent hospitalization was needed for febrile neutropenia or for other chemotherapy-related side effects.

As a single agent and administered conventionally in a short infusion, etoposide was associated with less than a 10% response rate in prostate cancer patients.[8,9] Fractionation of its administration significantly improved the response rate in patients treated for small cell lung carcinoma.[10] The toxicity and pharmacokinetics of oral etoposide are similar to those of the intravenous formulation.[11] The fraction of orally administered drug absorbed is approximately 50–60%. Thus the oral form allows for continuous dosing, i.e., "hyperfractionation." Numerous data have been published concerning tolerance of and clinical interest in oral etoposide in heavily pretreated patients with small cell lung cancer, breast carcinoma,

germ cell tumors, and non-Hodgkin's lymphoma. Most studies indicated that long term daily administration of oral etoposide may be superior to the conventional intravenous schedule, with manageable toxicity.[12]

Assuming that polychemotherapy increased tumor response rate compared with single-agent administration, we combined etoposide with an alkylating agent. Our choice was based on the synergistic effect of alkylating agents such as cisplatin[13,14] or estramustine[6] and etoposide. However, oral platinum derivatives are not available. Estamustine is a well known combination of estradiol and nitrogen mustard, which demonstrated a 10–40% response rate in metastatic prostate carcinoma.[15] Although recent studies indicated that its antineoplastic activity seems to be independent of its hormone and alkylating moieties and related to microtubule function and/or nuclear matrix interactions, we preferred cyclophosphamide, because 40% of included patients had previously received estrogen therapy (data not shown). Moreover, cyclophosphamide is largely active in adenocarcinomas and has demonstrated clinical efficacy in prostatic carcinoma.[16]

In our experience, a semicontinuous regimen of oral cyclophosphamide plus etoposide improved PS and relieved pain in 26% and 71% of patients, respectively. These clinical results were correlated with a decrease in PSA levels. Kelly et al.[17] have shown the prognostic value of PSA level decreases regarding median survival in metastatic HRPC after treatment, underscoring the role of PSA as an objective criterion of response. We have reported a 35% objective response rate for a mean duration of 8 months, including six partial responses and one complete response. Stabilization of the disease was obtained for 35% of patients. Thus 14 heavily pretreated patients (70%) benefitted by this oral chemotherapy regimen regardless of the number of hormonal therapy lines previously delivered. Objectively, the effect of flutamide withdrawal on response assessment could be incriminated in one case of partial response and reduced the response rate to 30%.

With comparable assessment criteria, this objective response rate appeared higher than those reported for oral etoposide alone. For Hussain et al.,[18] results were disappointing, with only two partial responses and two stabilizations among a group of 22 patients. Crawford et al.[5] reported preliminary data from a Phase II study conducted at the University of Colorado Health Sciences Center, which showed two short partial responses among seven evaluable patients. On the other hand, Pienta et al.[19] recently reported a 54% overall response rate with a 21 day regimen combining estramustine and etoposide, pointing out the synergistic effect between the two drugs. However, the authors, who had specified in a previous report that 27 patients among 42 discontinued flutamide 4 weeks before, did not detail the response rate according to the flutamide withdrawal. In this series, 31% of patients had received at least two lines of hormonal therapy, compared with 70% in our study. Moreover, similar median survival times were obtained in both trials. In our study, although the difference was not statistically significant, probably because of the small number of patients studied, 1 year overall survival seems better for responders than for nonresponders. There was no difference between the two groups in patient characteristics at inclusion. Thus, we could not isolate prognostic factors for response.

Our results are promising regarding intravenous chemotherapy. In fact, intravenous chemotherapy, including a large spectrum of drugs such as cisplatin,[20] Adriamycin and derivatives,[21] and suramin[22] failed to induce prolonged responses. Naito et al.[23] mentioned a 33% response rate with an intravenous etoposide, THP-Adriamycin, and cisplatin combination. However, in this trial, 40% of patients experienced WHO Grade 3–4 leukopenia and/or thrombocytopenia, impairing their quality of life. Finally, our results are as attractive as those previously obtained with somatostatin analogs in a comparable subset of patients.[24] In conclusion, oral cyclophosphamide plus etoposide may be an active and well tolerated regimen in HRPC and should be evaluated in a larger series.

REFERENCES

1. Klein LA. Prostatic carcinoma. *N Engl J Med* 1968;300:824–33.
2. Eisenberger MA, Simon R, O'Dwyer PJ, Wittes RE, Friedman MA. A reevaluation of nonhormonal cytotoxic chemotherapy in the treatment of prostatic carcinoma. *J Clin Oncol* 1985;3:827–41.
3. Henwood JM, Brogden RN. Etoposide: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in chemotherapy of cancer. *Drugs* 1990; 39:438–90.
4. Pienta KJ, Lehr JE. Inhibition of prostate cancer growth by estramustine and etoposide: evidence for interaction at the nuclear matrix. *J Urol* 1993;149:1622–5.
5. Crawford ED, Daneshgari F, Majeski SA. Etoposide in the treatment of hormone-refractory advanced carcinoma of the prostate. *Semin Oncol* 1992;19:53–7.
6. Pienta KJ, Redman BG, Hussain M, Esper P, Flaherty LE. Inhibition of prostate cancer growth by estramustine and etoposide. *Cancer* 1995;75:1920–6.
7. Yagoda A, Watson RC, Natale RB, Barzell W, Sogani P, Grabstald H, et al. A critical analysis of response criteria in patients with prostatic cancer treated with cis-diamminedichloride platinum II. *Cancer* 1979;44:1533–7.
8. Walther PJ, Williams SD, Troner M, Greco FA, Birch R, Einhorn LH, and the Southwestern Cancer Study Group. Phase II study of etoposide for carcinoma of the prostate. *Cancer Treat Rep* 1986;70:771–2.
9. Smart T, Hollander P, Yagoda A. Etoposide in prostatic cancer: experimental studies and Phase II trials in patients with bidimensionally measurable disease. *Cancer Chem Pharmacol* 1986;18:24–6.

10. Slevin ML, Clark PI, Joel SP, Malik S, Osborn RJ, Gregory WM, et al. A randomized trial to evaluate the effect of schedule on the activity of etoposide in small cell lung cancer. *J Clin Oncol* 1989;7:1333–40.
11. Hainsworth JD, Johnson DH, Frazier SR. Chronic daily administration of oral etoposide—a phase I trial. *J Clin Oncol* 1989;7:396–401.
12. Greco FA, Jonhson DH, Hainsworth JD. Chronic daily administration of oral etoposide. *Semin Oncol* 1990;17:71–4.
13. Shabel FM, Skipper HE, Trader MW, Laster WR, Griswold DP, Corbett TH. Establishment of cross-resistance profiles for new agents. *Cancer Treat Rep* 1983;42:905–7.
14. Seeber S, Osieka R, Schmidt CG, Achterrath W, Crooke ST. In vivo resistance toward anthracyclines, etoposide and cis-diamminedichloroplatinum (II). *Cancer Res* 1982;42:4719–21.
15. Murphy GP, Slack NH, Mittelaman A. Experiences with estramustine phosphate in prostate cancer. *Semin Oncol* 1983;10(Suppl):34–45.
16. Saxman S, Ansari R, Drasga R. Phase III of cyclophosphamide versus cyclophosphamide, doxorubicin, and methotrexate in hormone-refractory prostatic cancer. *Cancer* 1992;70:2488–92.
17. Kelly WK, Scher H, Mazumdar M, Vlamis V, Schwartz M, De Fossa S. Prostate-specific antigen as a measure of disease outcome in metastatic hormone refractory prostate cancer. *J Clin Oncol* 1993;11:607–15.
18. Hussain MH, Pienta KJ, Redman BG, Cummings GD, Flaherty LE. Oral etoposide in the treatment of hormone-refractory prostate cancer. *Cancer* 1994;74:100–3.
19. Pienta KJ, Redman B, Hussain M, Cummings G, Esper PS, Appel C, et al. Phase II evaluation of oral estramustine and oral etoposide in hormone-refractory adenocarcinoma of the prostate. *J Clin Oncol* 1994;12:2005–12.
20. Qazi R, Khandekar J. Phase II of cisplatin for metastatic prostatic carcinoma. An Eastern Cooperative Oncology Group study. *Am J Clin Oncol* 1983;6:203–6.
21. Rapoport BL, Falkson G. Phase II clinical study of pirarubicin in hormone-resistant prostate cancer. *Invest New Drugs* 1992;10:119–21.
22. Myers C, Cooper M, Stein C, LaRocca R, Walther MM, Weiss G. Suramin: a novel growth factor antagonist with activity in hormone-refractory prostate cancer. *J Clin Oncol* 1992;10:881–9.
23. Naito S, Ueda T, Kotoh S, Kumazawa J, Itoh K, Sagiyama K, et al. Treatment of advanced hormone-refractory prostate carcinoma with a combination of etoposide, pirarubicine and cisplatine. *Cancer Chemother Pharmacol* 1995;35:225–9.
24. Maulard C, Richaud P, Droz JP, Jessueld D, Dufour-Esquerre F, Housset M. Phase I–II study of the somatostatin analogue Lanreotide in hormone—refractory prostate cancer. *Cancer Chemother Pharmacol* 1995;36:259–62.